Notice/Disclaimer: The clinical information contained herein is provided for the express purpose of aiding the Pharmacy and Therapeutics ("P&T") Committee members in reviewing medications for inclusion in or exclusion from the Virginia Preferred Drug List. This information is not intended nor should it be used as a substitute for the expertise, skill, and judgment of physicians, pharmacists, or other healthcare professionals. The absence of a warning for any given drug or drug combination should not be construed to indicate that the drug or drug combination is safe, appropriate or effective for any given patient. This information is intended to supplement the knowledge and additional resources available to the P&T Committee members and should not be considered the sole criteria used by the P&T Committee in deciding what medications will be included or excluded from the Virginia Preferred Drug List.

- First-generation sulfonylureas include acetohexamide (Dymelor®), chlorpropamide (Diabinese®), tolazamide (Tolinase®), and tolbutamide (Orinase®). These drugs are not as commonly prescribed any more because the newer second-generation sulfonylureas offer advantages in side effect profiles and have less drug interactions.

- Second-generation sulfonylureas include glimepiride (Amaryl®), glipizide (Glucotrol®), Glipizide ER (Glucotrol XL®), and glyburide (Diabeta®, Glynase®, Micronase®). These drugs are all similarly effective in lowering blood sugar levels; the maximal blood sugar-lowering capability of all second-generation sulfonylureas is comparable. Some minor differences do exist between the second-generation sulfonylureas. Glipizide produces a more rapid lowering of blood sugar compared to glyburide. However, glyburide is more potent than glipizide (lower doses of glyburide are generally needed compared to glipizide). Glimepiride and glipizide ER are longer acting than the other two sulfonylureas (they can generally be taken once daily instead of twice daily like glyburide and glipizide).

Characteristic	**Glimepiride**	**Glipizide**		**Glyburide**	
		Prompt Release	**Extended Release**	**Non-Micronized**	**Micronized**
	Amaryl®	Glucotrol®	Glucotrol XL®	Diaßeta®/Micronase®	Glynase PresTab®
Pharmacology	Sulfonylureas stimulate the release of insulin from functioning beta cells and improve insulin sensitivity of peripheral tissues.[1] In animal studies, glimepiride was 2.5 to 3.5 times more potent at lowering blood glucose than glyburide. Glimepiride also had a more rapid onset of action and longer duration of action. *In vitro* studies have been performed in attempts to identify the mechanisms for the more rapid onset and longer duration with few definitive conclusions. Glimepiride and glyburide do appear to differ with respect to binding site association and dissociation rates and also appear to bind different components of the sulfonylurea receptor complex.[3-8] Extrapancreatic mechanisms in the improvement of glucose tolerance have also been described in several additional studies.[9,10]				
Date of FDA Approval	Nov 1995	May 1984	Apr 1994	May 1984	Mar 1992
Generic available?	No	Yes	No	Yes	Yes
Patient Expiration (if single source)	Apr 2005		Jan 2014		
Manufacturer (if single source)	Aventis		Pfizer		
Dosage forms / route of admin	Tablets – 1mg, 2mg, 4mg	Tablets: 5 mg, 10 mg	Tablets: 5 mg, 10 mg	Tablets – 1.25mg, 2.5mg, 5mg	Tablets: 1.5 mg, 3 mg, 4.5 mg, 6 mg
Dosing frequency	Once daily	Once daily to BID	Once daily	Once daily or BID	Once daily or BID
General dosing guidelines	▪ 1 to 4 mg once daily. Maximum maintenance dose is 8 mg once daily. Those patients who may be	▪ 5 – 15 mg once daily. At doses >15 mg daily, divided doses are recommended. Maximum daily does is	▪ 5 – 10 mg daily. While some patients may require 20 mg daily, there is not usually any benefit for doses >10 mg	▪ 2.5 – 20 mg daily. Those patients who may be more sensitive to the hypoglycemic effects should be started on 1.25	▪ 1.5 – 12 mg daily. Those patients who may be more sensitive to the hypoglycemic effects should be started on 0.75

Characteristic	Glimepiride	Glipizide		Glyburide	
		Prompt Release	Extended Release	Non-Micronized	Micronized
	Amaryl®	Glucotrol®	Glucotrol XL®	Diaßeta ®/Micronase®	Glynase PresTab®
	more sensitive to the hypoglycemic effects of glimepiride should be started on 1 mg once daily.	40 mg daily. Those patients who may be more sensitive to the hypoglycemic effects should be started on 2.5 mg once daily.	daily.	mg once daily	mg once daily
Pediatric Labeling	Safety and efficacy in children has not been established				
FDA Labeled Indications	adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone. AMARYL may be used concomitantly with metformin when diet, exercise, and AMARYL or metformin alone do not result in adequate glycemic control.	adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.		adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone. Glyburide may be used concomitantly with metformin when diet and glyburide or diet and metformin alone do not result in adequate glycemic control	
Other Studied Uses	No other significant studied uses; chlorpropamide, another sulfonylurea, has been used in the treatment of diabetes insipidus				
Contraindications	▪ Known Hypersensitivity ▪ Diabetic Ketoacidosis, with or without coma ▪ Type I DM ▪ severe hepatic or renal disease ▪ Contraindicated in pregnancy and lactation				
Drug interactions	▪ Highly protein bound drugs ▪ Miconazole ▪ Propranolol	▪ Highly protein bound drugs ▪ Miconazole ▪ Fluconazole ▪ Cyclosporine		▪ Highly Protein bound drugs ▪ Fluoroquinolones ▪ Coumadin ▪ Miconazole	

Characteristic	Glimepiride	Glipizide		Glyburide	
		Prompt Release	Extended Release	Non-Micronized	Micronized
	Amaryl®	Glucotrol®	Glucotrol XL®	Diaßeta ®/Micronase®	Glynase PresTab®
				▪ TCA ▪ Rifampin ▪ Fluconazole ▪ Gemfibrozil	
Major AEs / Warnings	▪ Hypoglycemia ▪ GI reactions – cholestatic jaundice and hepatitis ▪ Dermatologic reactions ▪ Hematologic reactions ▪ Disulfiram like reaction not reported with Amaryl in PI ▪ SIADH ▪ Nausea, dizzy, headache, asthenia ▪ Pregnancy Category C	▪ Hypoglycemia ▪ GI reactions – cholestatic Jaundice ▪ Dermatologic Reactions ▪ Hematologic Reactions ▪ Low incidence of disulfiram like-like reaction ▪ SIADH ▪ Hepatic porphyria ▪ Headache, dizziness, drowsiness ▪ Glucotrol XL ▪ Pregnancy Category C ▪ **XL**: GI disease-reduced GI retention times may influence pharmacokinetics and efficacy		▪ Hypoglycemia ▪ GI reactions – cholestatic Jaundice, Hepatitis ▪ Dermatologic Reactions – allergic skin reactions ▪ Hematologic Reactions ▪ Less disulfiram –like reaction than 1st generation ▪ SIADH ▪ Hepatic porphyria ▪ Pregnancy Category B	
Pharmacokinetics issues	▪ Food has no effect on absorption	▪ Absorption is delayed with food – recommend to take 30 minutes prior to a meal	▪ Food has no effect on absorption ▪ Less peak to trough variation than glipizide BID dosing	Food has no effect on absorption	▪ Food has no effect on absorption ▪ Dosing is not bioequivalent to glyburide – need to re-titrate
Tmax (h)	2-3	1-3	6-12	2-3	4
Protein Binding (%)	> 99.5	98-99	98-99	99	99
Half-life (h)	5-9.2	2-5	2-5	10	10
Duration	24 hr	10-24 hr		16-24 hr	12-24 hr
Active Metabolites	Yes (1/3 activity)	no	no	No (1/40th and 1/400th the activity of glyburide)	no
Key Populations	**Race.** No pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of AMARYL				

Characteristic	Glimepiride	Glipizide		Glyburide	
		Prompt Release	Extended Release	Non-Micronized	Micronized
	Amaryl®	Glucotrol®	Glucotrol XL®	Diaßeta ®/Micronase®	Glynase PresTab®
	(glimepiride tablets) in patients with NIDDM, the antihyperglycemic effect was comparable in whites (n = 536), blacks (n = 63), and Hispanics (n = 63). **Nursing Mothers:** Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered. **Geriatric Use**: There were no overall differences in effectiveness or safety between younger and older patients, but greater sensitivity of some individuals cannot be ruled out. As such, it should be noted that elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly. In addition, in elderly, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.				

Biguanides		
Characteristic	**Glucophage® (metformin)**	**Glucophage XR® (metformin extended-release)**
Pharmacology	Chemically and pharmacologically unique from other antihyperglycemics. Metformin decreases hepatic glucose secretion, decreases intestinal absorption of glucose and improves insulin sensitivity. Metformin as monotherapy should not cause hypoglycemia (unless patient is malnourished or has deficient caloric intake).	
Manufacturer	Bristol-Myers Squibb (brand product)	Bristol-Myers Squibb
Date of FDA approval	December 29, 1994	October 13, 2000
Generic available?	Yes	No
Dosage forms / route of admin	500 mg, 850 mg and 1000 mg oral tablets	500 mg extended-release oral tablets
Dosing frequency	QD-BID	Generally QD
General Dosing guidelines	Adults - starting dose – 500 mg BID or 850 mg QD with meals - maximum dose – 2550 mg/day Pediatrics - starting dose – 500 mg BID with meals - maximum dose – 2000 mg/day	Adults - starting dose – 500 mg QD with the evening meal - maximum dose – 2000 mg/day Pediatrics - no dosing indicated for Glucophage XR in children
Pediatric Labeling	10 years and up	17 years and up
FDA Labeled Indications	• As monotherapy, as an adjunct to diet and exercise to improve glycemic control in patients = 10 years of age with type 2 diabetes. • In combination with a sulfonylurea or insulin to improve glycemic control in adults = 17 years of age.	• As monotherapy, as an adjunct to diet and exercise to improve glycemic control in patients = 17 years of age with type 2 diabetes. • In combination with a sulfonylurea or insulin to improve glycemic control in adults = 17 years of age.
Other studied uses	• Type 1 diabetes • Polycystic ovarian syndrome • Prophylaxis of gestational diabetes in patients with insulin resistance and polycystic ovarian syndrome. • Obesity in patients with hyperinsulinemia • Prevention of diabetes in patients with impaired glucose tolerance	
Contraindications	• Renal disease or dysfunction (Scr = 1.5 mg/dL in males, = 1.4 mg/dL in females) • CHF requiring pharmacologic treatment • Patients receiving IV iodinated contrast agents (which can cause acute changes in renal function), should have metformin temporarily discontinued • Hypersensitivity to metformin • Acute or chronic metabolic acidosis (including DKA)	

Biguanides		
Characteristic	**Glucophage® (metformin)**	**Glucophage XR® (metformin extended-release)**
Drug interactions	Alcohol, cimetidine, furosemide, iodinated contrast material, nifedipine	
Major AEs/Warnings	• Most common – diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache • Lactic acidosis – rare, increased risk in patients with unstable of acute CHF, increased age, decreased renal function • Hepatic function impairment – can be associated with lactic acidosis, use not recommend in patients with clinical or laboratory evidence of hepatic impairment • Elderly – use in not recommended in patients = 80 years of age (unless CLcr indicates no decrease in renal function) • Surgery – temporarily discontinue if there will be restrictions on oral intake, can resume once oral intake and renal function are normal • Hypoxic states – shock, acute CHF, acute MI, etc – can predispose to lactic acidosis • Hypoglycemia – usually not observed if on metformin as monotherapy • Vitamin B12 – can see decreased levels – with or without overt anemia – if observed then discontinue metformin or supplement B12 • Pregnancy: Category B • Use not recommended in lactating women.	
Pharmacokinetics issues/ Special populations	• Food slightly delays and decreases the extent of absorption • No hepatic metabolism or biliary excretion • Excreted unchanged in the urine • Renal excretion is decreased and the half-life is increased in proportion to any decreases in renal function (CLcr)	• Food increases the AUC by about 50% - no change seen with Cmax and Tmax. • No hepatic metabolism or biliary excretion • Excreted unchanged in the urine • Cmax is 20% lower with Glucophage ER, but the AUC is similar to the regular release (the AUC with Glucophage ER is similar to the same total daily dose of the regular release administered BID) • Patients may switch from the regular release tablet to the extended-release at the same total daily dose.
	• In clinical studies there have been no differences observed in the hypoglycemic effects in Type 2 diabetics based on race.	
Place in therapy	Metformin is considered a first-line therapy for adults with Type 2 diabetes. It especially useful in overweight patients where the primary etiology of their diabetes is thought to be insulin resistance – metformin is not associated with weight gain like that observed with other oral agents. Metformin can also be an option for patients who skip meals frequently or experience episodes of hypoglycemia on low dose sulfonylureas. Metformin decreases triglycerides and LDL-cholesterol, HDL-cholesterol may increase slightly. The decreases in HgbA1C achieved with metformin are 1.5-2.0%, this is comparable to the reductions seen with sulfonylureas.	

Thiazolidinediones		
Characteristic	**Avandia® (rosiglitazone)**	**Actos® (pioglitazone)**
Pharmacology	Thiazolidinediones are very selective agonists for the peroxisome proliferators-activated receptor-gamma (found in adipose, the liver and skeletal muscle). They improve glucose control without reducing insulin levels. They inhibit hepatic gluconeogenesis and increase insulin sensitivity in muscle and adipose tissue. Their mechanism of action is dependent on the presence of insulin.	
Manufacturer	GlaxoSmithKline	Takeda Pharmaceuticals
Date of FDA approval	May 28, 1999	July 16, 1999
Dosage forms / route of admin	Tablets – 2 mg, 4 mg, 8 mg	Tablets – 15 mg, 30 mg, 45 mg
Dosing frequency	QD-BID	QD
General Dosing guidelines	• Starting dose – 4 mg QD (or divided BID) • Maximum dose ▪ 8 mg as monotherapy or if used in combination with metformin ▪ 4 mg if used in combination with a sulfonylurea or insulin	• Starting dose – 15mg to 30 mg QD • Maximum dose – 45 mg QD
Pediatric Labeling	Use in pediatric patients < 18 years of age is not recommended	
FDA Labeled Indications	• Monotherapy – as adjunct to diet and exercise to lower blood glucose concentrations in patients with type 2 diabetes • Combination therapy - with metformin, insulin or a sulfonylurea when diet, exercise and a single agent did not adequately control blood glucose levels. If a patient is on the maximum dose of a sulfonylurea or metformin and requires additional therapy, Avandia should be added to (not substituted for) the metformin or sulfonylurea	• Monotherapy – as adjunct to diet and exercise to lower blood glucose concentrations in patients with type 2 diabetes • Combination therapy - with metformin, insulin or a sulfonylurea when diet, exercise and a single agent did not adequately control blood glucose levels.
Other studied uses	Polycystic ovarian syndrome	Werner syndrome
Contraindications	Hypersensitivity to the medication or any of its components.	
Drug interactions	Rosiglitazone is metabolized predominantly by CYP2C8 and some by CYP2C9.	Pioglitazone is metabolized in part by CYP3A4.

Thiazolidinediones		
Characteristic	**Avandia® (rosiglitazone)**	**Actos® (pioglitazone)**
Major AEs/Warnings	• Only effective in the presence of insulin – not indicated for use in Type I diabetes. • Edema – use with caution in patients with edema. This can exacerbate or lead to CHF – monitor patients at risk. • Not recommended for use in patients with NYHA Class 3 or 4 CHF. • Weight gain – thought to involve fluid retention and fat accumulation. • Small decrease in hemoglobin – may be related to increased plasma volume. No significant hematologic clinical effects. • Ovulation may resume in premenopausal anovulatory patients. • Since structurally similar to troglitazone, pre-treatment and periodic LFTs are recommended (every other month for the first year and periodically thereafter). • Not recommended for use in patients with clinical evidence of active liver disease or increased transaminase levels (ALT more than 2.5 times the ULN)	
	• Mean increases in total cholesterol, LDL, HDL	Mean decreases in triglycerides and increases in HDL.
Pharmacokinetics issues	• Food delays time to Tmax, no change in extent of absorption. Can be taken with or without food. • Results of a population pharmacokinetic analysis including subjects of white, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.	• Food delays time to Tmax and decrease Cmax, no change in extent of absorption. Can be taken with or without food. • Pharmacokinetic data among various ethnic groups not available in labeling.
Dosage adjustment in key populations	• Hepatic function impairment (moderate to severe) – decreased clearance. Cmax, AUC and t1/2 all increased. Avandia use not recommended. • Dosage adjustment is not necessary in patients with renal insufficiency. • In geriatric patients (> age 65) Cmax and AUC were decreased by 35%, half-life and Tmax were similar - dosage adjustment is not necessary in geriatric patients.	• Hepatic function impairment (moderate to severe) – decreased Cmax, but no change in AUC. Use not recommended. • Dosage adjustment is not necessary in patients with renal insufficiency. • Dosage adjustment is not necessary in geriatric patients – no clinically relevant differences in pharmacokinetic parameters.
Place in therapy	• As a class, the mean decrease in HgbA1c with the thiazolidinediones is 0.5 to 1%. In monotherapy studies, both agents produced similar reductions in HgbA1c. Can be used alone or in combination with metformin, sulfonylureas, or insulin. Consider for use in patients requiring greater than 1.0 units of insulin/kg body weight/day or with clinical evidence of insulin resistance, and who are not candidates for or do not tolerate insulin. • Troglitazone was removed from the market on March 21, 2000.	

MEGLITINIDES		
Characteristic	**Nateglinide (Starlix)**	**Repaglinide (Prandin)**
Pharmacology	Amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This is dependent on functioning beta cells in the pancreas.	Closes ATP-dependent potassium cells in beta-cells of the pancreas. This leads to insulin secretion. This action is dependent on functioning beta cells in the pancreas. Insulin release is dependent on glucose levels – decreasing with lower glucose levels.
Manufacturer	Novartis	Novo Nordisk
Date of Approval	December 22, 2000	December 23, 1997
Generic available?	No	No
Dosage forms / route of admin	Tablets – 60mg, 120mg	Tablets – 0.5mg, 1mg, 2mg
Dosing frequency	TID	TID
General Dosing Guidelines	• Starlix should be taken 1 to 30 minutes before meals. • Recommended starting and maintenance dose is 120 mg TID before meals. The 60 mg dose may be used for patients near their blood glucose goal.	• Prandin should be taken 1 to 30 minutes before meals. • Dose range 0.5 mg to 4 mg with meals (2-4 times a day). • Maximum dose = 16 mg/day.
Pediatric Labeling	The safety and effectiveness in pediatric patients have not been established.	
FDA Labeled Indications	• Monotherapy to lower blood glucose in patients with Type 2 diabetes whose hyperglycemia cannot be adequately controlled by diet and physical exercise and who have not been chronically treated with other anti-diabetic agents. • In combination with metformin. In patients whose hyperglycemia is inadequately controlled with metformin, Starlix may be added to, but not substituted for, metformin.	• Monotherapy – as adjunct to diet and exercise to lower blood glucose concentrations in patients with type 2 diabetes • Combination with metformin or thiaolidinediones
Other Studied Uses	No other significant studied uses.	
Contraindications	• Know hypersensitivity to the drug or inactive ingredients • Type 1 diabetes • Diabetic ketoacidosis.	
Drug interactions	• Starlix is a potential inhibitor of CYP2C9	• Prandin is metabolized by the CYP3A4 enzyme system • Antifungal agents (ketoconazole, miconazole), erythromycin, – inhibit Prandin metabolism • CYP3A4 inducers – increase Prandin metabolism

MEGLITINIDES		
Characteristic	**Nateglinide (Starlix)**	**Repaglinide (Prandin)**
Major AEs / Warnings	• Most common –diarrhea, nausea, URI, hypoglycemia • Caution in moderate to severe liver disease • Pregnancy: Category C • Not recommended for use in lactating women	• Most common –arthralgia, GI effects (including nausea, vomiting, diarrhea, constipation), URI, hypoglycemia • Moderate to severe liver disease • Pregnancy: Category C • Not recommend for use in lactating women
Pharmacokinetics issues	• Absorption – rapid • T1/2 = 1.5 hours • Metabolized – CYP2C9 (70%) and CYP3A4 (30%) • Onset = 15 minutes • Peak response = 1-2 hours • Duration = 4 hours	• Absorption – rapid • T1/2 = 1 hour • Metabolized – CYP3A4 • Onset = 305 minutes • Peak response = 60-90 minutes • Duration = less than 4 hours
Dosage adjustment in key populations	• No adjustments necessary for patients with mild hepatic impairment or mild to severe renal impairment. • Decreased overall drug expose in dialysis patients. • No special adjustments are usually necessary for Geriatric patients, but they may be more susceptible to hypoglycemia	• Caution in chronic liver disease, extend dosing interval of patients with impaired liver function • Caution in renal impairment or failure – No dosing adjustments necessary for mild to moderate renal dysfunction. Use 0.5 mg as the starting dose if severe renal dysfunction (CrCL 20-40 mL/min). • No special adjustments are usually necessary for Geriatric patients, but they may be more susceptible to hypoglycemia

ALPHA-GLUCOSIDASE INHIBITORS		
Characteristic	**Precose® (acarbose)**	**Glyset® (miglitol)**
Pharmacology	Alpha-glucosidase inhibitors delay the digestion of ingested carbohydrates. This results in smaller increases observed in post-prandial blood glucose concentrations. Alpha-glucoside inhibitors do not enhance insulin secretion.	
Manufacturer	Bayer	Pfizer
Date of FDA approval	September 6, 1995	December 18, 1996
Generic available?	No	No
Dosage forms / route of admin	25 mg, 50 mg, 100 mg tablets for oral administration	25 mg, 50 mg, 100 mg tablets for oral administration
Dosing frequency	TID	TID
General Dosing guidelines	Initial dose – 25 mg TID (with first bite of each meal) Maintenance dose – 50 mg TID Maximum dose – 100 mg TID (for patients > 60 kg)	Initial dose – 25 mg TID (with first bite of each meal) Maintenance dose – 50 mg TID Maximum dose – 10 mg TID
Pediatric Labeling	Safety and efficacy in children have not been established.	
FDA Labeled Indications	• Monotherapy as an adjunct to diet to lower blood glucose in patients with Type 2 diabetes mellitus whose hyperglycemia cannot be managed on diet alone. • May also be used with a sulfonylurea when diet plus alpha-glucosidase inhibitor or a sulfonylurea do not produce adequate glucose control. • May also be used in combination with diet and insulin or diet and metformin.	• Monotherapy as an adjunct to diet to lower blood glucose in patients with Type 2 diabetes mellitus whose hyperglycemia cannot be managed on diet alone. • May also be used with a sulfonylurea when diet plus alpha-glucosidase inhibitor or a sulfonylurea do not produce adequate glucose control.
Other studied uses	• Type I diabetes • Dumping Syndrome • Acarbose may prevent the development of diabetes in patients with impaired glucose tolerance (based on the STOP-NIDDM trial)	• Type I diabetes

ALPHA-GLUCOSIDASE INHIBITORS		
Characteristic	**Precose® (acarbose)**	**Glyset® (miglitol)**
Contraindications	• Hypersensitivity to acarbose or any of its components • Diabetic ketoacidosis • Inflammatory bowel disease • Colonic ulceration • Partial intestinal obstruction, or predisposition to intestinal obstruction • Chronic intestinal diseases associated with marked disorders of digestion or absorption • Conditions that may deteriorate as a result of increased gas formation in the intestine • cirrhosis	• Hypersensitivity to miglitol or any of its components • Diabetic ketoacidosis • Inflammatory bowel disease • Colonic ulceration • Partial intestinal obstruction, or predisposition to intestinal obstruction • Chronic intestinal diseases associated with marked disorders of digestion or absorption • Conditions that may deteriorate as a result of increased gas formation in the intestine
Drug interactions	Digoxin, digestive enzymes, intestinal absorbants (eg, charcoal), fluoroquinolones	Digoxin, digestive enzymes, intestinal absorbants (eg, charcoal), propranolol, ranitidine, slight decreases in AUC and Cmax for glyburide and metformin (decreases were not statistically significant), fluoroquinolones
Major AEs/Warnings	• Most common – flatulence, diarrhea, abdominal pain • Less common - hypersensitivity reactions such as rash, elevations in AST/ALT (monitoring recommended every 3 months for the first year and periodically thereafter) • Use not recommended in patients with significant renal dysfunction (Cr > 2 mg/dL) • Concurrent use with a sulfonylurea may result in hypoglycemia • Oral absorption of sucrose is delayed, use glucose if hypoglycemia occurs • Pregnancy: Category B • Use not recommended in breastfeeding women	• Most common – flatulence, diarrhea, abdominal pain, rash • Less common – low serum iron (usually not persistent and not associated with decreases in Hgb or changes in hematologic indices • Use not recommended in patients with significant renal dysfunction (Cr > 2 mg/dL) • Concurrent use with a sulfonylurea may result in hypoglycemia • Oral absorption of sucrose is delayed, use glucose if hypoglycemia occurs • Pregnancy: Category B • Use not recommended in breastfeeding women

ALPHA-GLUCOSIDASE INHIBITORS		
Characteristic	**Precose® (acarbose)**	**Glyset® (miglitol)**
Pharmacokinetics issues	• Metabolized within the GI tract (primarily by intestinal bacteria) – this causes low systemic bioavailability of the parent drug. • AUC and Cmax were 1.5 times higher in elderly patients – this increase was not statistically significant. • There were significant increases in AUC and Cmax observed for patients with severe renal impairment.	• Absorption is not linear, but becomes saturated at high doses – 100% of a 25 mg dose is absorbed but only 50-70% of a 100 mg dose is absorbed. • No metabolism – miglitol is excreted as unchanged drug in the urine. • Plasma levels of more than double were observed in patients with CLcr < 25 ml/min. Since miglitol acts locally, altered dosages cannot correct for the increased plasma concentrations.
Place in therapy	The alpha-glucosidase inhibitors have a smaller effect on HgbA1C when compared to the other oral agents. Their primary use is to lower postprandial glucose levels; they only have minimal impact on fasting glucose levels. They typically do not cause hypoglycemia and by lowering postprandial spikes in blood glucose levels, they may contribute to the prevention of diabetic complications (especially cardiovascular-related complications. The theoretical advantage of miglitol over acarbose is a slightly lower incidence of GI side effects. However, the incidence of GI side effects is high with both medications and can make either medication difficult for patients to tolerate. The average reduction in HgbA1C is 0.5-1.0% for monotherapy (so will be more commonly seen in combination with a sulfonylurea). This class may be a good alternative (for monotherapy) in the subset of patients who only exhibit postprandial glucose elevations and have fasting levels within the desired range and are prone to hypoglycemia on sulfonylureas.	

Combination Products			
Characteristic	**Second-Generation Sulfonylurea + Metformin**		**Thiazolidinedione + Metformin**
	Glyburide/Metformin	**Glipizide/Metformin**	**Rosiglitazone/Metformin**
	Glucovance®	Metaglip®	Avandamet®
Pharmacology	Sulfonylureas stimulate the release of insulin from functioning beta cells. Metformin predominantly decreases hepatic glucose production but also decreases intestinal absorption of glucose, and improves insulin sensitivity. Unlike sulfonylureas, metformin does not usually produce hypoglycemia in patients with type 2 diabetes.		Metformin predominantly decreases hepatic glucose production. Thiazolidinediones predominantly improve insulin sensitivity of peripheral tissues Both metformin and thiazolidinediones inhibit hepatic gluconeogenesis, and reduce circulating insulin levels. Metformin decreases intestinal absorption of glucose
Date of FDA Approval	Jul 2000	Oct 2002	Oct 2002
Generic available?	No	No	No
Patient Expiration (if single source)		There are no unexpired patents for this product in the Orange Book Database. Exclusivity ends Oct 2005	
Manufacturer (if single source)	Bristol-Myers Squibb	Bristol-Myers Squibb	GlaxoSmithKline
Dosage forms / route of admin	Tablets 1.25 mg/ 250 mg 2.5 mg / 500 mg 5 mg / 500 mg	Tablets 2.5 mg/ 250 mg 2.5 mg / 500 mg 5 mg / 500 mg	Tablets 1 mg / 500 mg 2 mg / 500 mg 4 mg / 500 mg
Dosing frequency	Once daily to BID	Once daily to BID	Once daily or BID

Combination Products			
Characteristic	**Second-Generation Sulfonylurea + Metformin**		**Thiazolidinedione + Metformin**
	Glyburide/Metformin	**Glipizide/Metformin**	**Rosiglitazone/Metformin**
	Glucovance®	Metaglip®	Avandamet®
General dosing guidelines	▪ *GLUCOVANCE As Initial Therapy* ▪ Recommended starting dose: 1.25 mg/250 mg once or twice daily with meals. ▪ Dosage increases should be made in increments of 1.25 mg/250 mg per day every two weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose. ▪ In clinical trials of GLUCOVANCE as initial therapy, there was no experience with total daily doses greater than 10 mg/2000 mg per day. ▪ GLUCOVANCE 5 mg/500 mg should not be used as initial therapy due to an increased risk of hypoglycemia. ▪ *GLUCOVANCE Use in Previously Treated Patients (Second-Line Therapy)* ▪ Recommended starting dose: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals. ▪ For patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin alone, the	▪ *METAGLIP as Initial Therapy* ▪ For patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of METAGLIP is 2.5 mg/250 mg once a day with a meal. ▪ For patients whose FPG is 280 to 320 mg/dL a starting dose of METAGLIP 2.5 mg/500 mg twice daily should be considered. ▪ Dosage increases to achieve adequate glycemic control should be made in increments of one tablet per day every two weeks up to maximum of 10 mg/1000 mg or 10 mg/2000 mg METAGLIP per day given in divided doses. ▪ In clinical trials of METAGLIP as initial therapy, there was no experience with total daily doses greater than 10 mg/2000 mg per day. ▪ *METAGLIP as Second-Line Therapy* ▪ For patients not adequately controlled on either glipizide (or another sulfonylurea) or metformin alone, the recommended starting dose of METAGLIP is 2.5 mg/500 mg or 5mg/500mg twice daily with the morning and evening meals.	▪ *AVANDAMET as Initial Therapy* ▪ The safety and efficacy of AVANDAMET as initial therapy for patients with type 2 diabetes mellitus have not been established ▪ *AVANDAMET as Second-Line Therapy* ▪ For patients inadequately controlled on metformin monotherapy: the usual starting dose of AVANDAMET is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already being taken ▪ For patients inadequately controlled on rosiglitazone monotherapy: the usual starting dose of AVANDAMET is 1000 mg metformin (total daily dose) plus the dose of rosiglitazone already being taken ▪ When switching from combination therapy of rosiglitazone plus metformin as separate tablets: the usual starting dose of AVANDAMET is the dose of rosiglitazone and metformin already being taken. ▪ If additional glycemic control is needed: the daily dose of AVANDAMET may be increased by increments of 4 mg rosiglitazone and/or 500 mg metformin, up to the maximum recommended total daily dose of 8 mg/2000 mg. ▪ No studies have been performed specifically examining the safety and efficacy of AVANDAMET in patients previously treated with other oral hypoglycemic agents and switched to AVANDAMET.

Combination Products			
Characteristic	**Second-Generation Sulfonylurea + Metformin**		**Thiazolidinedione + Metformin**
	Glyburide/Metformin	**Glipizide/Metformin**	**Rosiglitazone/Metformin**
	Glucovance®	Metaglip®	Avandamet®
	recommended starting dose of GLUCOVANCE is 2.5 mg/500 mg or 5 mg/500 mg twice daily with the morning and evening meals. ▪ In order to avoid hypoglycemia, the starting dose of GLUCOVANCE should not exceed the daily doses of glyburide or metformin already being taken. The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg per day.	▪ In order to avoid hypoglycemia, the starting dose of METAGLIP should not exceed the daily doses of glipizide or metformin already being taken. ▪ The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg per day.	
Pediatric Labeling	Safety and efficacy in children has not been established		

Combination Products			
Characteristic	**Second-Generation Sulfonylurea + Metformin**		**Thiazolidinedione + Metformin**
	Glyburide/Metformin	**Glipizide/Metformin**	**Rosiglitazone/Metformin**
	Glucovance®	Metaglip®	Avandamet®
FDA Labeled Indications	• GLUCOVANCE is indicated as initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone. • GLUCOVANCE is indicated as second-line therapy when diet, exercise, and initial treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes. • For patients requiring additional therapy, a thiazolidinedione may be added to GLUCOVANCE to achieve additional glycemic control.	• METAGLIP is indicated as initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone. • METAGLIP is indicated as second-line therapy when diet, exercise, and initial treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes.	• AVANDAMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are already treated with combination rosiglitazone and metformin or who are not adequately controlled on metformin alone.
Other Studied Uses	▪ No other significant studied uses; chlorpropamide, another sulfonylurea, has been used in the treatment of diabetes insipidus		

Combination Products			
Characteristic	**Second-Generation Sulfonylurea + Metformin**		**Thiazolidinedione + Metformin**
	Glyburide/Metformin	**Glipizide/Metformin**	**Rosiglitazone/Metformin**
	Glucovance®	Metaglip®	Avandamet®
Contraindications	Metformin • Renal disease or dysfunction (Scr = 1.5 mg/dL in males, = 1.4 mg/dL in females) • CHF requiring pharmacologic treatment • Patients receiving IV iodinated contrast agents (which can cause acute changes in renal function), should have metformin temporarily discontinued • Hypersensitivity to metformin ▪ Acute or chronic metabolic acidosis (including DKA)		
	▪ Sulfonylurea ▪ Known Hypersensitivity ▪ Diabetic Ketoacidosis, with or without coma ▪ Type I DM ▪ severe hepatic or renal disease ▪ Contraindicated in pregnancy and lactation		▪ Rosiglitazone ▪ Hypersensitivity to the medication or any of its components
Drug interactions	▪ Metformin ▪ Alcohol, cimetidine, furosemide, iodinated contrast material, nifedipine		
	▪ Sulfonylurea: Highly protein bound drugs ▪ Miconazole ▪ Propranolol ▪ Fluconazole ▪ Cyclosporine		▪ In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. ▪ Rosiglitazone (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinylestradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Combination Products			
Characteristic	**Second-Generation Sulfonylurea + Metformin**		**Thiazolidinedione + Metformin**
	Glyburide/Metformin	**Glipizide/Metformin**	**Rosiglitazone/Metformin**
	Glucovance®	Metaglip®	Avandamet®
Major AEs / Warnings	Metformin ▪ Most common – diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache ▪ Lactic acidosis – rare, increased risk in patients with unstable of acute CHF, increased age, decreased renal function ▪ Hepatic function impairment – can be associated with lactic acidosis, use not recommend in patients with clinical or laboratory evidence of hepatic impairment ▪ Elderly – use in not recommended in patients = 80 years of age (unless CLCr indicates no decrease in renal function) ▪ Surgery – temporarily discontinue if there will be restrictions on oral intake, can resume once oral intake and renal function are normal ▪ Hypoxic states – shock, acute CHF, acute MI, etc – can predispose to lactic acidosis ▪ Hypoglycemia – usually not observed if on metformin as monotherapy ▪ Vitamin B12 – can see decreased levels – with or without overt anemia – if observed then discontinue metformin or supplement B12 ▪ Pregnancy: Category B ▪ Use not recommended in lactating women.		
	Sulfonylurea ▪ Hypoglycemia ▪ GI reactions – cholestatic Jaundice ▪ Dermatologic Reactions ▪ Hematologic Reactions ▪ Low incidence of disulfiram like-like reaction ▪ SIADH ▪ Hepatic porphyria ▪ Headache, dizziness, drowsiness ▪ Pregnancy Category C		Rosiglitazone ▪ Only effective in the presence of insulin – not indicated for use in Type I diabetes. ▪ Edema – use with caution in patients with edema. This can exacerbate or lead to CHF – monitor patients at risk. ▪ Not recommended for use in patients with NYHA Class 3 or 4 CHF. ▪ Weight gain – thought to involve fluid retention and fat accumulation. ▪ Small decrease in hemoglobin – may be related to increased plasma volume. No significant hematologic clinical effects. ▪ Ovulation may resume in premenopausal anovulatory patients.\ ▪ Since structurally similar to troglitazone, pre-treatment and periodic LFTs are recommended. ▪ Not recommended for use in patients with clinical evidence of active liver disease or increased transaminase levels (ALT more than 2.5 times the ULN)
Pharmacokinetics issues	▪ Refer to individual monographs		

<table>
<tr><th colspan="4">Combination Products</th></tr>
<tr><th rowspan="3">Characteristic</th><th colspan="2">Second-Generation Sulfonylurea + Metformin</th><th>Thiazolidinedione + Metformin</th></tr>
<tr><th>Glyburide/Metformin</th><th>Glipizide/Metformin</th><th>Rosiglitazone/Metformin</th></tr>
<tr><th>Glucovance®</th><th>Metaglip®</th><th>Avandamet®</th></tr>
<tr><td rowspan="2">Key Populations</td><td colspan="3">Metformin
Race:
• No studies of metformin pharmacokinetic parameters according to race have been performed.
• In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n = 249), blacks (n = 51) and Hispanics (n = 24).
Geriatric Patients:
• Results of a population pharmacokinetics analysis (n = 716 <65 years; n = 331>65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.
• Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged and Cmax is increased, compared to healthy young subjects.
• Change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.
• Metformin treatment and therefore treatment with AVANDAMET should not be initiated in patients > 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced</td></tr>
<tr><td colspan="2">Race:
• No information is available on race differences in the pharmacokinetics of either glyburide or glipizide.

Geriatric Patients
• No information is available on differences in the pharmacokinetics of either glyburide or glipizide in elderly patients.</td><td>Race:
• Results of a population pharmacokinetic analysis including subjects of white, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

Geriatric Patients:
• Results of a population pharmacokinetics analysis (n = 716 <65 years; n = 331>65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.</td></tr>
</table>

Drug Saf. 2000 Apr;22(4):313-20.

Comparative tolerability of sulphonylureas in diabetes mellitus.

Harrower AD.

Department of Medicine and Bracco House Diabetes Centre, Monklands Hospital, Airdrie, Lanarkshire, Scotland.

The sulphonylurea drugs have been the mainstay of oral treatment for patients with diabetes mellitus since they were introduced. In general, they are well tolerated, with a low incidence of adverse effects, although there are some differences between the drugs in the incidence of hypoglycaemia. Over the years, the drugs causing the most problems with hypoglycaemia have been chlorpropamide and glibenclamide (glyburide), although this is a potential problem with all sulphonylureas because of their action on the pancreatic beta cell, stimulating insulin release.

Other specific problems have been reported with chlorpropamide that occur only rarely, if at all, with other sulphonylureas. Hyponatraemia secondary to inappropriate antidiuretic hormone activity, and increased flushing following the ingestion of alcohol, have been well described. The progressive beta cell failure with time results in eventual loss of efficacy, as these agents depend on a functioning beta cell and are ineffective in the absence of insulin-producing capacity. Differences in this secondary failure rate have been reported, with chlorpropamide and gliclazide having lower failure rates than glibenclamide or glipizide. The reasons for this are unclear, but the more abnormal pattern of insulin release produced by glibenclamide may be partly responsible and, indeed, may explain the increased risk of hypoglycaemia with this agent.

Previously reported increased mortality associated with tolbutamide therapy has not been substantiated, and more recent data have shown no increased mortality from sulphonylurea treatment. Indeed, benefit from glycaemic control, regardless of the agent used--insulin or sulphonylurea--was reported by the United Kingdom Prospective Diabetes Study. Nevertheless, there is still ongoing controversy in view of the experimental evidence, mainly from animal studies, of potential adverse effects on the heart from sulphonylureas, but these are difficult to extrapolate into clinical situations. Most of these studies have been carried out with glibenclamide, which makes comparison of possible risk difficult. Other cardiovascular risk factors may be modified by gliclazide, which seems unique among the sulphonylureas in this respect. Its reported haemobiological and free radical scavenging activity probably resides in the azabicyclo-octyl ring structure in the side chain. Reduced progression or improvement in retinopathy has been reported in comparative trials with other sulphonylureas, and the effect is unrelated to improvements in glycaemia.

There are differences between the sulphonylureas in some adverse effects, risk of hypoglycaemia, failure rates and actions on vascular risk factors. As a group of drugs, they are very well tolerated, but differences in overall tolerability can be identified.

Am J Med Sci. 2000 Mar;319(3):143-8.

Comparative efficacy and potency of long-term therapy with glipizide or glyburide in patients with type 2 diabetes mellitus.

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Department of Medicine, The University of Tennessee-Memphis 38163, USA.

BACKGROUND: Long-term studies on the comparative efficacy and relative potency of glipizide and glyburide are sparse and controversial.

METHODS: In a randomized prospective trial, we compared the effectiveness and relative potency of glipizide and glyburide over a 15-month period in 18 patients with type 2 diabetes mellitus (DM2) (9 on glyburide and 9 on glipizide) who were unresponsive to diet therapy. Glycemic control was assessed using 4 methods: 1) quarterly fasting plasma glucose (FPG), and 2-hour postprandial plasma glucose after a standard breakfast; 2) insulin and glucose response to Sustacal (test meal) challenge every 3 to 6 months; 3) quarterly hemoglobin A1c; and 4) intravenous glucose tolerance testing every 6 months to measure first and second phase insulin secretion. Patient characteristics were similar in each treatment group.

RESULTS: Similar doses of glipizide (11 mg/day) or glyburide (10 mg/day) resulted in comparable reduction of FPG and hemoglobin A1c and increase in first phase insulin response to intravenous glucose tolerance testing. There was greater reduction in FPG and 2-hour postprandial plasma glucose with glipizide than with glyburide in 6 months. Contrary to the Physicians' Desk Reference, but consistent with another short-term study, our long-term study demonstrated that glipizide and glyburide are equipotent at similar doses in controlling hyperglycemia in DM2.

CONCLUSIONS: Glipizide and glyburide are effective in controlling hyperglycemia with similar doses in DM2. Glipizide exhibits greater reduction in FPG and 2PPG at 6 months. Additional studies are needed to validate equipotency of these drugs.

Hosp Pharm. 1995 Jun;30(6):467-9, 472-4.

Formulary conversion from glipizide to glyburide: a cost-minimization analysis.

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Economic pressure prompted us to search for and implement cost-saving strategies at Bronx Municipal Hospital. This paper describes a cost-minimization analysis of the impact of formulary substitution of glyburide for glipizide on glycemic control, safety, and costs. In 76 patients with computerized prescription records, switching from a mean daily glipizide dose of 19 mg to a mean daily glyburide dose of 10.2 mg did not affect glycemic control. A subset of 33 elderly patients experienced only three drug-related adverse events during the 2-year observation period. The conversion program yielded a 51% reduction in overall expenditures for oral hypoglycemic agents between 1991 and 1993. These findings indicate that our conversion program was successful, which has led to its becoming a model for other New York City municipal outpatient pharmacies.

Lancet. 1998 Sep 12;352(9131):837-53.

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group.

BACKGROUND: Improved blood-glucose control decreases the progression of diabetic microvascular disease, but the effect on macrovascular complications is unknown. There is concern that sulphonylureas may increase cardiovascular mortality in patients with type 2 diabetes and that high insulin concentrations may enhance atheroma formation. We compared the effects of intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with type 2 diabetes in a randomised controlled trial.

METHODS: 3867 newly diagnosed patients with type 2 diabetes, median age 54 years (IQR 48-60 years), who after 3 months' diet treatment had a mean of two fasting plasma glucose (FPG) concentrations of 6.1-15.0 mmol/L were randomly assigned intensive policy with a sulphonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin, or conventional policy with diet. The aim in the intensive group was FPG less than 6 mmol/L. In the conventional group, the aim was the best achievable FPG with diet alone; drugs were added only if there were hyperglycaemic symptoms or FPG greater than 15 mmol/L. Three aggregate endpoints were used to assess differences between conventional and intensive treatment: any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death); all-cause mortality. Single clinical endpoints and surrogate subclinical endpoints were also assessed. All analyses were by intention to treat and frequency of hypoglycaemia was also analysed by actual therapy.

FINDINGS: Over 10 years, haemoglobin A1c (HbA1c) was 7.0% (6.2-8.2) in the intensive group compared with 7.9% (6.9-8.8) in the conventional group--an 11% reduction. There was no difference in HbA1c among agents in the intensive group. Compared with the conventional group, the risk in the intensive group was 12% lower (95% CI 1-21, p=0.029) for any diabetes-related endpoint; 10% lower (-11 to 27, p=0.34) for any diabetes-related death; and 6% lower (-10 to 20, p=0.44) for all-cause mortality. Most of the risk reduction in the any diabetes-related aggregate endpoint was due to a 25% risk reduction (7-40, p=0.0099) in microvascular endpoints, including the need for retinal photocoagulation. There was no difference for any of the three aggregate endpoints between the three intensive agents (chlorpropamide, glibenclamide, or insulin). Patients in the intensive group had more hypoglycaemic episodes than those in the conventional group on both types of analysis (both p<0.0001). The rates of major hypoglycaemic episodes per year were 0.7% with conventional treatment, 1.0% with chlorpropamide, 1.4% with glibenclamide, and 1.8% with insulin. Weight gain was significantly higher in the intensive group (mean 2.9 kg) than in the conventional group (p<0.001), and patients assigned insulin had a greater gain in weight (4.0 kg) than those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg).

INTERPRETATION: Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes.

Diabetes Care. 1994 Jan;17(1):45-9.

Long-term randomized placebo-controlled double-blind therapeutic comparison of glipizide and glyburide. Glycemic control and insulin secretion during 15 months.

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Hormone Laboratory, Aker Hospital, Oslo, Norway.

OBJECTIVE--To examine the long-term (15 months) effects on glycemic control and insulin secretion of glipizide and glyburide treatment in patients with non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS--Prospective, randomized, double-blind, placebo-controlled study on 46 NIDDM patients comparing fasting levels and test-meal responses of glucose and insulin during 15 months of follow-up.

RESULTS--A comparable reduction in HbA1c levels by both agents versus placebo was observed throughout the study period, but after a marked initial reduction in both sulfonylurea groups, all three groups showed gradually increasing HbA1c levels. However, both glipizide and glyburide achieved and maintained lowered postprandial glucose levels and increased fasting and postprandial insulin levels compared with placebo.

CONCLUSIONS--Both glipizide and glyburide may achieve and maintain glycemic reduction and stimulation of insulin secretion during long-term treatment. However, these agents do not prevent the gradual increase in overall glycemia that develops over time in NIDDM patients.

N Engl J Med. 1995 Aug 31;333(9):541-9.

Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group.

DeFronzo RA, Goodman AM.

Diabetes Division, University of Texas Health Science Center, San Antonio, TX 78284, USA.

BACKGROUND: Sulfonylurea drugs have been the only oral therapy available for patients with non-insulin-dependent diabetes mellitus (NIDDM) in the United States. Recently, however, metformin has been approved for the treatment of NIDDM.

METHODS: We performed two large, randomized, parallel-group, double-blind, controlled studies in which metformin or another treatment was given for 29 weeks to moderately obese patients with NIDDM whose diabetes was inadequately controlled by diet (protocol 1: metformin vs. placebo; 289 patients), or diet plus glyburide (protocol 2: metformin and glyburide vs. metformin vs. glyburide; 632 patients). To determine efficacy we measured plasma glucose (while the patients were fasting and after the oral administration of glucose), lactate, lipids, insulin, and glycosylated hemoglobin before, during, and at the end of the study.

RESULTS: In protocol 1, at the end of the study the 143 patients in the metformin group, as compared with the 146 patients in the placebo group, had lower mean (+/- SE) fasting plasma glucose concentrations (189 +/- 5 vs. 244 +/- 6 mg per deciliter [10.6 +/- 0.3 vs. 13.7 +/- 0.3 mmol per liter], $P < 0.001$) and glycosylated hemoglobin values (7.1 +/- 0.1 percent vs. 8.6 +/- 0.2 percent, $P < 0.001$). In protocol 2, the 213 patients given metformin and glyburide, as compared with the 210 patients treated with glyburide alone, had lower mean fasting plasma glucose concentrations (187 +/- 4 vs. 261 +/- 4 mg per deciliter [10.5 +/- 0.2 vs. 14.6 +/- 0.2 mmol per liter], $P < 0.001$) and glycosylated hemoglobin values (7.1 +/- 0.1 percent vs. 8.7 +/- 0.1 percent, $P < 0.001$). The effect of metformin alone was similar to that of glyburide alone. Eighteen percent of the patients given metformin and glyburide had symptoms compatible with hypoglycemia, as compared with 3 percent in the glyburide group and 2 percent in the metformin group. In both protocols the patients given metformin had statistically significant decreases in plasma total and low-density lipoprotein cholesterol and triglyceride concentrations, whereas the values in the respective control groups did not change. There were no significant changes in fasting plasma lactate concentrations in any of the groups.

CONCLUSIONS: Metformin monotherapy and combination therapy with metformin and sulfonylurea are well tolerated and improve glycemic control and lipid concentrations in patients with NIDDM whose diabetes is poorly controlled with diet or sulfonylurea therapy alone.

Expert Opin Investig Drugs. 2003 Jul;12(7):1179-87.

Thiazolidinediones -- some recent developments.

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The role of thiazolidinediones (currently rosiglitazone and pioglitazone) in the treatment of Type 2 diabetes is firmly established. The mechanism of action involves binding to the peroxisome proliferator-activated receptor-gamma, a transcription factor that regulates the expression of specific genes especially in fat cells but also other cell types such as endothelial cells, macrophages and monocytes, vascular smooth muscle cells and colonic epithelium. Thiazolidinediones have been shown to interfere with expression and release of mediators of insulin resistance originating in adipose tissue (e.g., increased free fatty acids, decreased adiponectin) in a way that results in net improvement of insulin sensitivity (i.e., in muscle and liver).

A direct or indirect effect on AMP-dependent protein kinase may also be involved. Prevention of lipid accumulation in tissues critical to glycaemia such as visceral adipocytes, liver, muscle and beta-cells at the expense of lipids accumulating at the less harmful subcutaneous site may be central to their net metabolic effect. The sustained beneficial effect of troglitazone on beta-cell function in women with previous gestational diabetes in addition to the insulin-sensitizing properties point to an important role of this class of drugs in the prevention of Type 2 diabetes. Original safety concerns based on animal and in vitro studies (e.g., fatty bone marrow transformation, colonic cancer, adipogenic transdifferentiation of blood cells) remain theoretical issues but become less pressing practically with prolonged uneventful clinical use.

Hepatotoxicity for troglitazone and fluid retention, which can aggravate pre-existing heart failure, are the most important side effects. In summary, with the thiazolidinediones, a novel concept for the treatment of insulin resistance and possibly preservation of beta-cell function is available that could become effective in the prevention of Type 2 diabetes. Moreover, their anti-inflammatory properties also make them interesting in the prevention and treatment of atherosclerosis and possibly other inflammatory conditions (e.g., inflammatory bowel disease). Long-term data will be necessary for a final risk-benefit assessment of these substances.

Arterioscler Thromb Vasc Biol. 2003 Oct 1;23(10):1744-9.

Thiazolidinediones and blood lipids in type 2 diabetes.

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We evaluated study population characteristics and treatment effects on blood lipids between studies in which either rosiglitazone (RSG) or pioglitazone (PIO) was investigated in patients with type 2 diabetes. We performed a summary analysis of all published double-blind, placebo-controlled studies with RSG (4 and 8 mg/d) and PIO (15, 30, and 45 mg/d). Data were analyzed by the random-effects model. Nineteen trials met our inclusion criteria, yielding 5304 patients, 3236 in studies with RSG and 2068 in studies with PIO.

Subjects treated with PIO were more obese and showed more pronounced hyperglycemia and dyslipidemia (increased triglycerides and decreased HDL cholesterol) at baseline than did subjects treated with RSG. By weighted linear-regression analysis, studies with PIO showed greater beneficial effects on triglycerides, total cholesterol, and LDL cholesterol, after adjustment for the respective lipid levels at baseline. RSG 8 mg/d showed greater increases in total cholesterol and LDL cholesterol than did RSG 4 mg/d. PIO 30 mg/d showed greater reductions in triglycerides than did PIO 15 mg/d.

Studies conducted with PIO showed more beneficial effects on blood lipids, but also different study population characteristics in comparison with studies conducted with RSG. Differences in both pharmacologic properties between agents and study population characteristics are likely to have influenced the results.

Diabetes Care. 2002 Apr;25(4):708-11.

A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone.

Khan MA, St Peter JV, Xue JL.

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OBJECTIVE: To characterize potential differences in glycemic control, plasma lipid level, and weight in a cohort of patients previously treated with troglitazone (TROG) who were switched to either pioglitazone or rosiglitazone.

RESEARCH DESIGN AND METHODS: After a 2-week washout from TROG, 186 patients were randomly assigned to receive either pioglitazone (PIO) or rosiglitazone (ROSI). Weight, HbA(1c), and fasting lipid profile were documented before discontinuing TROG and at 4 months after starting either pioglitazone or rosiglitazone. Secondarily, the effect of concurrent medications on study outcomes was assessed.

RESULTS: A total of 127 patients completed follow-up: 67 individuals in the PIO group (32 women, 35 men) and 60 individuals in the ROSI group (33 women, 27 men). There were no significant differences in gender mix, age, weight, fasting lipid profile, or HbA(1c) between the ROSI and PIO groups. After 4 months of randomized treatment, no change in HbA(1c) from baseline between or within groups was noted. Both groups experienced an equal and significant increase in weight from baseline of approximately 2.0 kg. Thiazolidinedione and HMG-CoA reductase inhibitor therapy had significant and independent effects on lipid profile ($P < 0.005$). Significant improvements in lipid profile were noted in the PIO group ($P < 0.01$), whereas none were detected with conversion to ROSI. Specifically, the PIO group experienced an average decrease in total cholesterol of approximately 20 mg/dl.

CONCLUSIONS: Differing effects on lipid profile were apparent after random conversion from TROG to either PIO or ROSI, despite similar weight increase and glycemic control. The clinical significance of these differences remains to be determined, and further comparative research is warranted.

Endocr Pract. 2001 May-Jun;7(3):162-9.

Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice.

Gegick CG, Altheimer MD.

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OBJECTIVE: To compare short-term glycosylated hemoglobin (HbA(1c)), lipid, weight, tolerability, and hepatic effects after switching patients with type 2 diabetes from troglitazone to either pioglitazone or rosiglitazone treatment.

METHODS: This study compared the effects of conversion from maintenance troglitazone therapy to pioglitazone versus rosiglitazone. HbA(1c), lipids, weights, adverse effects, and hepatic status were monitored, providing no other major therapeutic change had been made. Of 163 study candidates, 144 and 125 patients fulfilled the criteria for comparison of HbA(1c) and lipids, respectively.

RESULTS: HbA(1c) decreased an absolute mean of 0.08% for each treatment group, after a mean 3.2-month observation. Mean cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol levels decreased in the pioglitazone group by 4.7%, 11.3%, and 7.3% but increased 8.4%, 38.4%, and 8.1%, respectively, in the rosiglitazone group. Mean high-density lipoprotein (HDL) increased 2.6% with pioglitazone and decreased 6.3% with rosiglitazone therapy. Patients receiving a statin concomitantly when switched to rosiglitazone treatment had a 51.9% mean triglyceride increase versus a 25.7% increase for those not taking a statin, whereas the patients switched to pioglitazone therapy had respective decreases of 14.2% and 6.2%. Both drugs were generally well tolerated; patients in both groups had similar slight weight increases and no hepatic dysfunction.

CONCLUSION: Patients switched from maintenance troglitazone treatment to either pioglitazone or rosiglitazone therapy had similar glycemic control. Conversion to pioglitazone therapy caused a trend toward improvement in all lipid variables, but switching to rosiglitazone therapy caused significantly increased levels of cholesterol, triglycerides, and LDL and a trend toward decreased HDL. Patients already receiving statins when switched to rosiglitazone therapy had particularly notable triglyceride worsening. Whether these effects will lead to changes in cardiovascular outcome or will be maintained over a longer period remains to be established.

Diabetes Care, April 2000 v23 i4 p557

A Comparison in a Clinical Setting of the Efficacy and Side Effects of Three Thiazolidinediones. (Brief Article)(Statistical Data Included)

Three thiazolidinediones (TZDs) are currently available for clinical use in the U.S.: troglitazone, rosiglitazone, and pioglitazone. Because we are aware of no comparative studies of these three agents, we wish to report our initial experience with their efficacy in lowering glucose and improving dyslipidemia, as well as their side effects.

When clinically indicated, patients were started consecutively on each of the three TZDs as they became available. Results from the TZD groups, each of which comprised [sim]50 patients, were reviewed. We excluded patients who were not on maximal recommended doses of TZDs; namely, 600 mg of troglitazone, 8 mg of rosiglitazone (twice a day for monotherapy), and 45 mg of pioglitazone. Patients were also excluded if they started during the observation period on a medication that would influence their lipid profile or weight. Only data at baseline and between 2 and 4 months of treatment were analyzed.

After exclusion, the total numbers of patients in each group, troglitazone, rosiglitazone, and pioglitazone were 35, 36, and 30, respectively. Their average ages were 60.1, 59.2, and 60.2 years; sex, 65, 50, and 38% male to total patients; weight, 89.7, 92.1, and 87.2 kg; and initial [HbA.sub.1c], 8.50, 8.73, and 8.72%. Patients were taking other medications for hyperglycemia treatment in 89, 76, and 81% of each group.

Table 1 compares the effect of each TZD. [HbA.sub.1c] was similarly reduced with each agent, especially when patients with an initial [HbA.sub.1c] [greater than]7.9% were studied. The magnitude of reduction reported is greater than that reported elsewhere [1] and may reflect the self-education and self-monitoring of blood glucose that is part of our program.

We observed that the beneficial effect on lipids was most with pioglitazone and least with rosiglitazone during this 2- to 4-month observation period. The average initial HDL cholesterol in each group, namely, troglitazone, rosiglitazone, and pioglitazone was 46.6, 43.1, and 50.7 mg/dl, respectively; LDL cholesterol was 109.1, 102.9, and 96.4 mg/dl, respectively; and the triglycerides were 223, 172, and 207 mg/dl, respectively. The lack of effect of rosiglitazone on triglycerides and the elevation of LDL cholesterol [2] and the beneficial effect on HDL and triglycerides of pioglitazone [3] have been previously reported.

In addition, the weight increase with pioglitazone was noticeably greater than that observed with the other two agents. However, the incidence of edema as the reason for discontinuing a medication was not greater with pioglitazone than with rosiglitazone. The weight gain cannot be explained on improvement of glucose control since all agents reduced the [HbA.sub.1c] equally. Perhaps the increase in weight is due to the increase in the number and size of adipocytes [4].

We conclude from our observations that each TZD appears equal in its glucose lowering ability, and thus, the selection of an agent is based on other factors, such as its lipid benefit and side effects. We look forward to larger and longer-term studies to confirm this finding and to compare the liver toxicity of each agent.

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Comparison of the effects of the three TZDs

	Troglitazone	Rosiglitazone	Pioglitazone
[HbA.sub.1c](%)	-1.57(34)	-1.89(25)	-1.93 (27)
Initial[HbA.sub.1c]>7.9%(%)	-2.37(19)	-2.66(18)	-2.54 (17)
HDL cholesterol(mg/dl)	1.5(17)	0.5(23)	6.5 (18)
LDL cholesterol(mg/dl)	7.2(17)	11.5(17)	-1.1 (17)
Triglycerides(mg/dl)	-5(17)	47(23)	-21 (17)
Weight(kg)	0.7(34)	0.5(25)	2.6 (26)
Edema	0(35)	3(38)	2 (30)
Other side effects	0(35)	5(38)	1 (30)

Ann Pharmacother. 2001 Nov;35(11):1426-34.

Nateglinide therapy for type 2 diabetes mellitus.

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OBJECTIVE: To review the pharmacology, pharmacokinetics, dosing guidelines, adverse effects, drug interactions, and clinical efficacy of nateglinide.

DATA SOURCES: Primary and review articles regarding nateglinide were identified by MEDLINE search (from 1966 to January 2001); abstracts were identified through the Institute for Scientific Information Web of Science (from 1995 to January 2001) and the American Diabetes Association; additional information was obtained from the nateglinide product information.

STUDY SELECTION/DATA EXTRACTION: All articles and meeting abstracts identified from the data sources were evaluated and all information deemed relevant was included in this review. Much of the information was from abstracts or the product labeling, since few clinical studies have been published in the medical literature.

DATA SYNTHESIS: Nateglinide is a novel nonsulfonylurea oral antidiabetic agent that stimulates insulin secretion from the pancreas. It has a rapid onset and short duration of action, allowing administration before a meal to reduce postprandial hyperglycemia. Improvement in glycemic control with nateglinide monotherapy has been demonstrated in patients not previously treated with antidiabetic medications. Greater improvement in glycemic control was observed when nateglinide was administered in combination with metformin.

CONCLUSIONS: Nateglinide is similar to repaglinide, but has a quicker onset of action, quicker reversal, and does not usually require dosage titration. Based on the pharmacodynamics of nateglinide and repaglinide, nateglinide produces a more rapid postprandial increase in insulin secretion, and its duration of response is shorter than that of repaglinide. The risk of postabsorptive hypoglycemia should be lower than with either sulfonylureas or repaglinide.

Diabetes, May 2000 v49 i5 pA128

Reduced Risk of Delayed Hypoglycemia with Nateglinide Compared to Repaglinide.

YULIA H. WALTER; LAURENCE BROOKMAN; PEIMING MA; JOHN E. GERICH; JAMES F. MCLEOD.

Nateglinide (NAT, A-4166) is a physiologic mealtime glucose regulator with a short-acting, glucose-sensitive effect on insulin secretion. The hypoglycemic potential of NAT relative to repaglinide (REP) was assessed in a double-blind, placebo-controlled crossover study. Eight overnight-fasted, type 2 diabetic males with mean [+ or -] SD age of 58 [+ or -] 9 yr and fasting plasma glucose (FPG) of 186 [+ or -] 45 mg/dl randomly received single doses of 120mg NAT, 2mg REP or placebo (PBO) at the start of a 2h hyperglycemic clamp at 54 mg/dl above FPG. Plasma glucose (PG), insulin and glucagon were measured during and for 4h after abruptly ending the clamp. Mean PG was 244 mg/dl just before the clamp ended, and was comparable for all treatments. Treatments were 7 days apart. [AUC.sub.x-y] = integrated response from hour x to y.

Treatment	Insulin [AUC.sub.0-1]	Insulin [AUC.sub.2-6]
NAT	26 [+ or -] 4([Alpha])	62 [+ or -] 8([Alpha])([Beta])
REP	21 [+ or -] 4	74 [+ or -] 10([Alpha])
PBO	15 [+ or -] 2	50 [+ or -] 6

Treatment	Glucose [AUC.sub.2-6]	Glucagon [AUC.sub.2-6]
NAT	605 [+ or -] 61([Alpha]) ([Beta])	319 [+ or -] 20([Beta])
REP	548 [+ or -] 52([Alpha])	376 [+ or -] 32([Alpha])
PBO	722 [+ or -] 53	315 [+ or -] 15

Treatment	Glucose [nadir.sub.2-6]
NAT	120 [+ or -] 12([Alpha])([Beta])
REP	93 [+ or -] 8([Alpha])
PBO	149 [+ or -] 12

(mean [+ or -] standard error; ([Alpha]) $p<0.05$ vs. PBO; ([Beta]) $p<0.02$ vs. REP by ANOVA or t-test).

Significantly more insulin was secreted early from 0-1h postdose after NAT vs. PBO, but was comparable between NAT and REP, and [is greater than] PBO, for the remainder of the 2h clamp. Over 2-6h postdose, NAT stimulated less insulin than REP after the clamp ended. After 2h postdose, plasma insulin declined more rapidly after NAT than REP and was not different from PBO by 3.7h postdose (NAT 13 [+ or -] 2; PBO 11 [+ or -] 1 [micro]U/ml. Insulin levels in the REP group remained elevated compared to PBO at 4h postdose (18 [+ or -] 2 vs. 11 [+ or -] 1 [micro]U/ml, p [is less than] 0.05). Consistent with this, PG declined more gradually after the clamp with NAT than REP. The PG nadir over 2-6h postdose occurred at 5h for both NAT and REP, but was lower after REP. There was no difference in glucagon levels after NAT and PBO, but the mean glucagon peak over 2-6h was higher after REP vs. NAT and PBO (REP 116 [+ or -] 14; NAT 93 [+ or -] 7; PBO 87 [+ or -] 4 pg/ml, p [is less than] 0.05), presumably in reaction to declining plasma glucose. Due to its faster onset and shorter duration of action, NAT offers a more physiological approach to glycemic control with less potential for delayed hypoglycemia than REP.

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Characteristic	Accolate® (zafirlukast)	Singulair® (montelukast sodium)
Pharmacology	Selective leukotriene receptor antagonists inhibit the cysteinyl leukotriene receptor. Cysteinyl leukotriene is associated with the pathophysiology of asthma and allergic rhinitis (ex. smooth muscle constriction and airway edema).	
Manufacturer	AstraZeneca	Merck
Date of FDA approval	September 26, 1996	February 20, 1998
Generic available	No	No
Dosage forms / route of admin	10 mg, 20 mg tablets for oral administration	• 10 mg tablets for oral administration • 4mg, 5 mg chewable tablets • 4 mg (packet) granules for oral administration (contents can be administered orally or mixed with soft foods – the contents should not be dissolved in liquids)
Dosing frequency	BID	QD
General Dosing guidelines	• Adults and children = 12 years of age - 20 mg bid • Children 5-11 years of age – 10 mg bid	• Adults and adolescents = 15 years of age – 10 mg qd • Children 6 to 14 years of age – 5 mg qd • Children 2 to 5 years of age – 4 mg qd • Children 12 to 23 months with asthma – 4 mg qd
Pediatric Labeling	5 years and older	12 months and older
FDA Labeled Indications	Prophylaxis and chronic treatment of asthma in adults and children 5 years of age and older.	• Prophylaxis and chronic treatment of asthma in adults and children 12 months of age and older. • Relief of symptoms of seasonal allergic rhinitis in adults and children 2 years of age and older.
Other studied uses	• Chronic urticaria • Exercised-induced bronchospasm	• Chronic urticaria • Exercised-induced bronchospasm
Contraindications	Hypersensitivity to zafirlukast or any of its components.	Hypersensitivity to montelukast or any of its components.
Drug interactions	Aspirin, Erythromycin, Theophylline, Warfarin	Phenobarbital, Rifampin

Characteristic	Accolate® (zafirlukast)	Singulair® (montelukast sodium)
Major AEs/Warnings	• Most common – headache, nausea, infection, • Less common - diarrhea, dizziness, ALT elevation • Zafirlukast should not be used for the reversal of acute asthma attacks. • Hypersensitivity reactions – including angioedema, urticaria, and rash • Eosinophilia – rare cases consistent with Churg-Strauss Syndrome • Liver disease • Pregnancy: Category B • Zafirlukast is excreted in breast milk and should not be used in nursing women.	• Most common – headache, abdominal pain, influenza, cough • Less common - dyspepsia, dizziness, ALT/AST elevation, fatigue, rash • Montelukast should not be used for the reversal of acute asthma attacks. • Eosinophilia – rare cases consistent with Churg-Strauss Syndrome • Chewable tablets contain phenylalanine • Use with caution in severe liver disease • Pregnancy: Category B • It is not known if montelukast is excreted in breast milk. Use with caution in nursing women.
Pharmacokinetics issues	• Take on an empty stomach - food decreases bioavailability by about 40%. In the elderly the Cmax and AUC are 2 to 3 times higher. • Hepatic function impairment causes decreased clearance of zafirlukast – Cmax and AUC are 50-60% greater. • No differences in the pharmacokinetics of zafirlukast due to race have been observed. • Onset = 30 minutes • Duration = 12 hours	• Half-life is slightly increased in the elderly – no dosing adjustment necessary. • Mild to moderate hepatic impairment increases AUC by about 40% and slightly increases half-life – no dosing adjustment necessary • Pharmacokinetic differences due to race have not been studied. • Onset = 3-4 hours • Duration = up to 24 hours
Dosage adjustment in key populations	• Renal impairment – no dosing adjustment necessary • Liver impairment – monitor for adverse effects and consider dosage adjustments if indicated	• Elderly – no dosing adjustment necessary • Renal impairment – no dosing adjustment necessary • Liver impairment (mild to moderate) – no dosing adjustment necessary

Characteristic	Accolate® (zafirlukast)	Singulair® (montelukast sodium)
Place in therapy	▪ Mild asthma - Leukotriene modifiers can be used as alternatives to inhaled corticosteroids and other treatments (according to EPR-2), particularly for those patients unable to use a metered-dose inhaler. This class is effective monotherapy for mild persistent asthma, however in comparison studies, neither agent is as effective as an inhaled corticosteroid in improving lung function. Improvement in lung function was generally 12-15% for the inhaled corticosteroids and 5-8% for the leukotriene modifiers. ▪ Leukotriene modifiers may be added to therapy with inhaled corticosteroids for patients not completely controlled. ▪ Leukotriene modifiers have been shown to be helpful in ameliorating reactions to aspirin in aspirin-sensitive patients. The reaction is not completely blocked, sensitive patients may still experience reactions, but at higher doses. ▪ Exercise induced asthma – Pre-treatment with a short-acting beta-agonist is recommended. If this does not control symptoms then a leukotriene modifier or a long-acting beta-agonist may be added. ▪ Allergic rhinitis – studies have not found a leukotriene modifier to be superior to antihistamines and have found nasal steroids to be more effective than a leukotriene modifier.	

Oral Montelukast Compared with Inhaled Salmeterol To Prevent Exercise-Induced Bronchoconstriction

A Randomized, Double-Blind Trial

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Background: Montelukast, an oral, once-daily leukotriene receptor antagonist, provides protection against exercise-induced bronchoconstriction.

Objective: To evaluate the effect of 8 weeks of therapy with salmeterol aerosol or montelukast on exercise-induced bronchoconstriction in adults with asthma.

Design: 8-week multicenter, randomized, double-blind study.

Setting: 17 asthma treatment centers in the United States.

Patients: 191 adults with asthma who had documented exercise-induced bronchoconstriction.

Intervention: Qualified patients were randomly assigned to double-blind treatment with montelukast (10 mg once in the evening) or salmeterol (50 µg [2 puffs] twice daily).

Measurements: Changes in pre-exercise and post-exercise challenge values; percentage inhibition in the maximal percentage decrease in FEV_1; the area above the FEV_1-time curve; and time to recovery of FEV_1 at days 1 to 3, week 4, and week 8 of treatment.

Results: By day 3, similar and statistically significant reductions in maximal percentage decrease in FEV_1 were seen with both therapies. Sustained improvement occurred in the montelukast group at weeks 4 and 8; at these time points, the bronchoprotective effect of salmeterol decreased significantly. At week 8, the percentage inhibition in the maximal percentage decrease in FEV_1 was 57.2% in the montelukast group and 33.0% in the salmeterol group ($P = 0.002$). By week 8, 67% of patients receiving montelukast and 46% of patients receiving salmeterol had a maximal percentage decrease in FEV_1 of less than 20%.

Conclusions: The bronchoprotective effect of montelukast was maintained throughout 8 weeks of study. In contrast, significant loss of bronchoprotection at weeks 4 and 8 was seen with salmeterol. Long-term administration of montelukast provided consistent inhibition of exercise-induced bronchoconstriction at the end of the 8-week dosing interval without tolerance.

*For members of the Exercise Study Group, see the Appendix.

Author and Article Information

From Merck & Co., Inc., West Point, PennsylvaniaAm. J. Respir. Crit. Care Med., Volume 159, Number 6, June 1999, 1814-1818

Randomized Placebo-controlled Study Comparing a Leukotriene Receptor Antagonist and a Nasal Glucocorticoid in Seasonal Allergic Rhinitis

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Allergic rhinitis is an inflammatory disorder associated with local leukotriene release during periods of symptoms. Therefore, it has been suggested that antileukotrienes may be beneficial in the treatment of this disease. Leukotriene receptor antagonists have recently become available for asthma treatment, but little is known of their effects on allergic rhinitis. We have evaluated the effects of the leukotriene receptor antagonist zafirlukast versus placebo in patients with allergic rhinitis during the grass pollen season, using the nasal glucocorticoid beclomethasone dipropionate (BDP) as a positive treatment control. Thirty-three patients with seasonal allergic rhinitis were in a double-blind, double-dummy fashion randomized to treatments with oral zafirlukast (20 mg twice a day), intranasal beclomethasone dipropionate (200 µg twice a day), or placebo. The treatment was initiated 3 wk prior to the expected beginning of the grass pollen season. Patients completed a daily symptom-score list for sneezing, rhinorrhea, nasal itch, and nasal blockage during the 50-d treatment period. Nasal biopsies for quantification of local tissue eosinophilia (immunohistochemistry; EG2) were taken 1 mo before initiation of treatment and immediately after the peak of grass pollen season. Patients receiving treatment with zafirlukast had degrees of nasal symptoms similar to those in the placebo group, whereas the BDP group had significantly less symptoms compared with both treatments ($p = 0.01$ and $p = 0.005$, respectively). The numbers of activated eosinophils in the nasal tissue increased significantly during the pollen season in both the zafirlukast and the placebo groups, but not in the BDP group. These results obtained with a limited number of patients do not support any clinical efficacy of regular treatment with an oral antileukotriene in seasonal allergic rhinitis but rather favor the use of a nasal glucocorticoid.

Am. J. Respir. Crit. Care Med., Volume 157, Number 6, June 1998, S238-S246

Summary of Clinical Trials with Zafirlukast

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Zafirlukast is an orally active and selective cysteinyl leukotriene (cysLT) receptor antagonist. In humans, zafirlukast antagonized the effects of exogenously administered LTD_4 and cysLTs released endogenously in response to physical and chemical stimuli. Zafirlukast antagonized LTD_4-induced bronchoconstriction, with effects still evident 12 h after drug administration. In clinical models of asthma, zafirlukast inhibited bronchospasm after allergen or exercise challenge in patients with asthma. In multicenter trials in patients with chronic, stable asthma, zafirlukast reduced asthma symptoms, decreased as-needed -agonist use, and improved pulmonary function without increasing the number of adverse events. Zafirlukast also exhibited evidence of an anti-inflammatory effect in the lung in preliminary studies involving segmental antigen challenge. The results from these clinical trials demonstrate that zafirlukast is effective and safe for the prophylactic treatment of asthma. Calhoun WJ. Summary of clinical trials with zafirlukast.

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United States Department of Veterans Affairs Pharmacy Benefits Management Strategic Healthcare Group. Leukotriene inhibitor criteria for use in veteran patients.

Oral Bisphosphonates for Osteoporosis

Characteristic	Fosamax (alendronate)	Actonel (risedronate)
Manufacturer	Merck	Procter and Gamble
Basic Pharmacology And Structural Differences	Alendronate and risedronate are nitrogen-containing bisphosphonates that have an affinity for hydroxyapatitie crystals in bone and induce an inhibition of osetoclast activity. They also decrease the number of available osteoclasts by inhibiting enzymes in the mevalonate pathway, which then prevents the production of the protein isoprenylation, a compound that is necessary for osteoclast formation.	
	Alendronate is classified as a second generation biphosphonate and is most similar chemically to pamidronate, differing from the latter only by an additional side-chain carbon.	Risedronate is considered a third-generation bisphosphonate due to its potency and specificity. The antiresorptive potency of the drug is considerably greater than that of both first-generation (etidronate, clodronate) and second-generation (alendronate, pamidronate, tiludronate) compounds; it is least 100 times as potent as pamidronate and alendronate, and over 1000 times as potent as etidronate. The drug is a pyridinyl bisphosphonate that is chemically similar to other bisphosphonates in terms of its basic phosphorus-carbon-phosphorus (P-C-P) structure; however, it contains a cyclic side chain, as opposed to the short alkyl side chains of etidronate and the amino terminal groups of pamidronate and alendronate
Date of FDA Approval	September 29, 1995 September 22, 2003 (Oral solution - not commercially available as of this writing)	March 27, 1998
Generic available?	No	No
Dosage forms / route of admin	Tablets: 5mg, 10mg, 35mg, 40mg and 70 mg Oral Solution: each bottle contains 70mg of alendronate The 70mg tablets and oral solution are equally bioavailable.	Tablets: 5mg, 30 mg, 35mg

Oral Bisphosphonates for Osteoporosis

Characteristic	Fosamax (alendronate)	Actonel (risedronate)
General Dosing Guidelines:	**Osteoporosis in postmenopausal women:** **Treatment:** 70 mg once weekly or 10 mg once daily. **Prevention:** 35 mg once weekly or 5 mg once daily. The safety of treatment and prevention of osteoporosis with alendronate has been studied for up to 7 years. **Osteoporosis in men**: 10 mg once daily. Alternatively, one 70 mg tablet once weekly may be considered. **Glucocorticoid-induced osteoporosis:** 5 mg once daily for men and women. For postmenopausal women not receiving estrogen, the recommended dose is 10mg once daily. **Paget disease of bone:** 40 mg once a day for 6 months for men and women. **Elderly:** No dosage adjustment is necessary. **Renal function impairment:** No dosage adjustment is necessary in patients with mild to moderate renal insufficiency (CLcr 35 to 60mL/minute). However, alendronate is not recommended for patients with more severe renal insufficiency (CLcr less than 35 mL/min) because of lack of experience. Patients also should receive adequate amounts of calcium and vitamin D.	**Treatment/Prevention of postmenopausal osteoporosis:** 5 mg orally taken daily or one 35 mg tablet orally taken once weekly. **Treatment/Prevention of glucocorticoid-induced osteoporosis:** 5 mg orally taken daily. **Paget disease:** 30 mg once daily for 2 months. Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs or if treatment fails to normalize serum alkaline phosphatase. For re-treatment, the dose and duration of therapy are the same as for initial treatment. No data are available on more than 1course of re-treatment. **Renal function impairment:** Risedronate is not recommended for use in patients with severe renal impairment (CLcr less than 30mL/min). No dosage adjustment is necessary in patients with a CLcr at least 30 mL/min or in the elderly. Patients also should receive adequate amounts of calcium and vitamin D.

Oral Bisphosphonates for Osteoporosis

Characteristic	Fosamax (alendronate)	Actonel (risedronate)
Administration	▪ Alendronate: Take in the morning with a full glass of plain water ≥ 30 minutes before the first meal, beverage, or medication. Patients should not lie down for 30 minutes after taking the medication. ▪ Oral solution: Drink one entire bottle of solution (70mg) followed by 2 ounces of plain water	▪ Risedronate: Take ≥ 30 minutes with plain water before the first food or drink of the day. Patients should not lie down for 30 minutes after taking the medication.
FDA Labeled Indications	▪ Treatment and prevention of osteoporosis in women ▪ Treatment to increase bone mass in men with Osteoporosis ▪ Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids ▪ Treatment of Paget's disease	▪ Treatment and prevention of osteoporosis in postmenopausal women ▪ Treatment and prevention of glucocorticoid-induced osteoporosis in men and women ▪ Treatment of Paget's disease
Pediatric Labeling	• Currently alendronate is not labeled for use in children. • 10/2003: Merck has submitted to the FDA 12-month safety and efficacy data from an ongoing study of the use of alendronate in children with osteogenesis imperfecta (OI).	• Risedronate pharmacokinetics have not been studied in patients < 18 years of age
Other studied uses	• None Primary Hyperparathyroidism • Hypercalcemia • Hypercalcemia of malignancy • Multiple myeloma	
Contraindications	▪ Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia ▪ Inability to stand or sit upright for at least 30 min ▪ Hypocalcemia ▪ Hypersensitivity	▪ Hypocalcemia ▪ Hypersensitivity ▪ Inability to stand or sit upright for at least 30 minutes
Drug interactions	▪ Absorption of bisphosphonates is decreased when given concurrently with meals, orange juice, coffee, milk products, calcium supplements/antacids/multivalent cations (eg, magnesium)	

Oral Bisphosphonates for Osteoporosis

Characteristic	Fosamax (alendronate)	Actonel (risedronate)
Major AEs / Warnings	▪ GI effects ▪ Esophageal, gastric and duodenal ulcers and rarely followed by esophageal stricture or perforation have been reported in patients receiving Fosamax. ▪ Used in caution in patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis or ulcers) ▪ Caution should be used during concomitant use of NSAIDs	▪ Bisphosphonates have been known to cause upper gastrointestinal disorders such as dysphagia, esophagitis and esophageal or gastric ulcers
Pregnancy Category	Both Actonel and Fosamax are C; only oral etidronate is pregnancy category B	
Pharmacokinetics issues	The terminal half-life is estimated to be 10 years	The terminal half-life is estimated to be 480 hours
Dosage adjustment in key populations	No adjustment in mild to moderate renal disease however, it is not recommended for patients with severe renal disease (CrCl < 35 mL/min)	
Pipeline Agents	▪ Boniva ™ : described in detail on next page : FDA approved, not yet marketed. ▪ OLPADRONATE: In limited published studies, olpadronate has been reported beneficial in children with osteogenesis imperfecta and in patients with bone metastases secondary to prostate cancer. ▪ Ospemifene, a novel selective estrogen receptor modulator (SERM) that has been show in clinical trials to have a potential for prevention and treatment of osteoporosis in postmenopausal women.	

Oral Bisphosphonates for Osteoporosis

Characteristic	Fosamax (alendronate)	Actonel (risedronate)

Summary

There are no head to head clinical trials of Fosamax versus Actonel; however, the Fosamax Actonel Comparison Trial (FACT), sponsored by Merck, and will be the first study to evaluate the effectiveness and tolerability of the two agents during 12 months of treatment in postmenopausal women with osteoporosis. Each study will examine approximately 800 postmenopausal women with osteoporosis defined by a bone mineral density (BMD) T-score of < -2.0. Recipients will be randomized in a one to one blinded fashion to either Fosamax 70mg once weekly or Actonel 35mg once weekly.

American Association of Clinical Endocrinologists 2001 Medical Guidelines for the Prevention and Management of Postmenopausal Osteoporosis

- Level 1 evidence of efficacy in reducing the risk of vertebral fractures is available for bisphosphonates (alendronate, risedronate), calcitonin, and raloxifene."
- Only bisphosphonates have been shown to reduce the risk of hip and other non-vertebral fractures in prospective trials (Level 1 evidence).

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. 2001

- Placebo-controlled RCTs of cyclic etidronate, alendronate, and risedronate analyzed by a systematic review and meta-analysis have revealed that all of these bisphosphonates increase BMD at the spine and hip in a dose-dependent manner.
- They consistently reduce the risk of vertebral fractures by 30% to 50%.
- Alendronate and risedronate reduce the risk of subsequent nonvertebral fractures in women with osteoporosis and adults with glucocorticoid-induced osteoporosis.
- There is uncertainty about the effect of antiresorptive therapy in reducing nonvertebral fracture in women without osteoporosis.

Efficacy Studies for both Actonel® and Fosamax® products have been shown in :

Primary prevention of vertebral Fractures
Secondary prevention of vertebral Fractures
Primary prevention of hip fractures
Secondary prevention of hip fractures
Prevention of glucocorticoid induced vertebral fractures

In a recent study sponsored by the NIH, combination therapy of Preos (a full length version of parathyroid hormone) plus Fosamax® did not provide synergy in increasing bone density any more than hormone alone.

From the VA PBM: "Alendronate and risedronate produce similar results with regard to treatment and prevention of osteoporosis, and treatment of steroid-induced osteoporosis. Although prevention of steroid induced osteoporosis and treatment of men with primary osteoporosis have only been shown with one of the drugs (risedronate and alendronate, respectively), these are class effects and equivalent outcomes would be expected."

Oral Bisphosphonates for Osteoporosis

Characteristic	Didronel® (Etidronate) (Please note the drug has been approved but has an off-label use in osteoporosis)	Boniva ™ (Ibandronate) (Please note the drug has been approved but not yet launched in the United States)
Manufacturer	Procter and Gamble	Roche (To be co-promoted by Roche and GlaxoSmithKline)
Basic Pharmacology And Structural Differences	Didronel acts primarily on bone. Its major pharmacologic action is the reduction of normal and abnormal bone resorption. Secondarily, it reduces bone formation since formation is coupled to resorption. This reduces bone turnover, but the reduction of bone turnover, *per se*, is not the important action in the reduction of hypercalcemia. Didronel's reduction of abnormal bone resorption is responsible for its therapeutic benefit in hypercalcemia. The antiresorptive action of Didronel has been demonstrated under a variety of conditions, although the exact mechanism(s) is not fully understood. The drug is more potent than etidronate but significantly less potent than the aminobisphosphonate, alendronate. Didronel does not contain a nitrogen group.	Boniva ™ (ibandronate sodium) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated Bone resorption. Boniva ™ (ibandronate sodium) Ibandronate, like other bisphosphonates, affects bone mineralization. In vitro, the bisphosphonates slow the formation of hydroxyapatite. Ibandronate is a very potent inhibitor of osteoclasts, which serves to prevent bone resorption and hypercalcemia.
Date of FDA Approval	APR 20, 1987	May 2003
Generic available?	No	No
Dosage forms / route of admin	**Tablets**: 200 mg and 400 mg	2.5 mg tablets: supplied as white, oblong, film-coated tablets,

Oral Bisphosphonates for Osteoporosis

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General Dosing Guidelines:	**Paget disease:** Initial treatment: 5 to 10 mg/kg/day (not to exceed 6 months) or 11 to 20 mg/kg/day (not to exceed 3 months). Reserve doses greater than 10mg/kg/day for use when lower doses are ineffective, when there is an overriding requirement for suppression of bone turnover (especially when irreversible neurologic damage is possible) prompt reduction of elevated cardiac output is required. Doses greater than 20 mg/kg/day are not recommended. Retreatment: Initiate only after an etidronate-free period of at least 90days and when there is biochemical, symptomatic, or other evidence of active disease process. Retreatment regimens are the same as for initial treatment. **Heterotopic ossification:** Spinal cord injury: 20 mg/kg/day for 2 weeks, followed by 10 mg/kg/day for 10 weeks; total treatment period is 12 weeks. Institute therapy as soon as feasible following the injury, preferably prior to evidence of heterotopic ossification. Total hip replacement: 20 mg/kg/day for 1 month preoperatively, then 20 mg/kg/day for 3 months postoperatively; total treatment period is 4 months. Retreatment has not been studied.	The recommended dose of Boniva™ for treatment and prevention of postmenopausal osteoporosis is one 2.5 mg film-coated tablet once daily. Patients also should receive adequate amounts of calcium and vitamin D

Oral Bisphosphonates for Osteoporosis

Characteristic	Didronel® (Etidronate) (Please note the drug has been approved but has an off-label use in osteoporosis)	Boniva ™ (Ibandronate) (Please note the drug has been approved but not yet launched in the United States)
Administration	Take on an empty stomach 2 hours before or after meals, including vitamin and mineral supplements or antacids, which are high in metals such as calcium, iron, magnesium, or aluminum.	Boniva™ should be taken at least 60 minutes before the first food or drink (other than water) of the day and before any oral medications containing multivalent cations (including antacids, supplements or vitamins). Boniva™ tablets should be swallowed whole with a full glass of plain water (6 to 9 oz) while the patient is standing or sitting upright. The patient should not lie down for 60 minutes after taking Boniva™.
FDA Labeled Indications	▪ For the treatment of symptomatic Paget disease of bone. ▪ Heterotopic ossification: Prevention and treatment following total hip replacement or spinal cord injury	Boniva ™ is indicated for the treatment and prevention of osteoporosis in postmenopausal women.
Pediatric Labeling	▪ Safety and efficacy has not been approved for use in children < 18 years of age; however, children have been treated with oral etidronate at doses recommended for adults to prevent heterotopic ossifications or soft tissue calcifications.	The pharmacokinetics of Boniva have not been studied in children < 18 years of age
Other studied uses	▪ Osteoporosis of various etiologies (found to be effective) (Treatment and prevention of osteoporosis in postmenopausal women; prevention of corticosteroid-induced osteoporosis) ▪ Metastatic bone pain ▪ Treatment of hypercalcemia	▪ Multiple myeloma ▪ Skeletal metastases ▪ Hypercalcemia of malignancy
Contraindications	▪ Clinically overt osteomalacia ▪ Known hypersensitivity ▪ Avoid use in patients with serum creatinine of 2.5 mg/dL or higher	▪ Known hypersensitivity to Boniva ™ or to any of its excipients ▪ Uncorrected hypocalcemia ▪ Inability to stand or sit upright for at least 60 minutes

Oral Bisphosphonates for Osteoporosis

Characteristic	Didronel® (Etidronate) (Please note the drug has been approved but has an off-label use in osteoporosis)	Boniva ™ (Ibandronate) (Please note the drug has been approved but not yet launched in the United States)
Drug interactions	▪ Antacids containing magnesium or aluminum may decrease the absorption of etidronate if taken concurrently. Their administration should be separated by at least two hours ▪ Calcium and iron containing drugs and foods may decrease the absorption if etidronate and separation by 2 hours should take place if administered together ▪ Warfarin : an increase in PT may occur when given in combination. Monitoring of PT should be done with concurrent administration.	▪ Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. ▪ Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron), including milk, food, and antacids are likely to interfere with absorption of ibandronate. ▪ Aspirin/Nonsteroidal Anti-inflammatory Drugs (NSAIDs) In the large, placebo-controlled osteoporosis Treatment Study, aspirin and nonsteroidal anti-inflammatory drugs were taken by 62% of the 2946 patients. Among aspirin or NSAID users, the incidence of upper gastrointestinal adverse events in patients treated with ibandronate 2.5 mg daily (28.9%) was similar to that in placebo-treated patients (30.7%). However, since aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with Boniva ™ .
Major AEs / Warnings	▪ Use with caution in patients with enterocolitis; diarrhea or increased bowel frequency are possible ▪ Avoid use in patients with serum creatinine of 2.5 mg/dL or higher ▪ Delay or interrupt therapy in patients with fractures ▪ History of hypoparathyroidism; risk of hypocalcemia	▪ Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preapproval clinical trials, including those conducted with Boniva ™ . Boniva ™ is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).
Pregnancy Category	Pregnancy Category C	Pregnancy Category C

Oral Bisphosphonates for Osteoporosis

Characteristic	Didronel® (Etidronate) (Please note the drug has been approved but has an off-label use in osteoporosis)	Boniva ™ (Ibandronate) (Please note the drug has been approved but not yet launched in the United States)
Pharmacokinetics issues	**Patients with Renal Impairment** Dosage adjustment suggested in patients with a serum creatinine of 2.5 to 4.9 mg/dL – if used at all	**Patients with Hepatic Impairment** No dose adjustment is necessary **Patients with Renal Impairment** No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 mL/min.
Dosage adjustment in key populations	See above	The bioavailability and pharmacokinetics in men and women appear to be the same. Pharmacokinetic differences due to race have not been studied. The only differences in the geriatric population are expected to relate to progressive age-related changes in renal function.
Pipeline Agents	See first chart for pipeline agents	
Summary	See first chart for summary/efficacy information.	

Available Products	FDA Indications						
	Heterotopic ossification	**Prevention of Osteoporosis in Post-menopausal women**	**Treatment of Osteoporosis Post-menopausal women**	**Treatment to Increase Bone Mass in Men with Osteoporosis**	**Treatment of Paget's Disease**	**Prevention of Glucocorticoid Induced Osteoporosis**	**Treatment of Glucocorticoid Induced Osteoporosis**
Alendronate (Fosamax Tablet)		X	X	X	X		X
Risedronate (Actonel Tablet)		X	X		X	X	X
Etidronate (Didronel Tablet)	X				X		
Ibandronate (Boniva Tablet)		X	X				

First Health Services Corporation

Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group.

Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, Nevitt MC, Suryawanshi S, Cummings SR; Fracture Intervention Trial.

J Clin Endocrinol Metab. 2000 Nov;85(11):4118-24.

Department of Epidemiology and Biostatistics, University of California, San Francisco 94105, USA. dblack@psg.ucsf.edu

We examined the effect of alendronate treatment for 3-4 yr on risk of new fracture among 3658 women with osteoporosis enrolled in the Fracture Intervention Trial. This cohort included women with existing vertebral fracture and those with osteoporosis as defined by T score of less than -2.5 at the femoral neck but without vertebral fracture. All analyses were prespecified in the data analysis plan. The magnitudes of reduction of fracture incidence with alendronate were similar in both groups. The two groups were, therefore, pooled to obtain a more precise estimate of the effect of alendronate on relative risk of fracture (relative risk, 95% confidence interval): hip (0.47, 0.26-0.79), radiographic vertebral (0.52, 0.42-0.66), clinical vertebral (0.55, 0.36-0.82), and all clinical fractures (0.70, 0.59-0.82). Reductions in risk of clinical fracture were statistically significant by 12 months into the trial. We conclude that reductions in fracture risk during treatment with alendronate are consistent in women with existing vertebral fractures and those without such fractures but with bone mineral density in the osteoporotic range. Furthermore, reduction in risk is evident early in the course of treatment. This pooled analysis provides a more precise estimate of the antifracture efficacy of alendronate in women with osteoporosis than that in prior reports.

First Health Services Corporation

Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group.

Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH 3rd, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD.
JAMA. 1999 Oct 13;282(14):1344-52.

University of California, San Francisco 94117-3608, USA.

CONTEXT: Risedronate, a potent bisphosphonate, has been shown to be effective in the treatment of Paget disease of bone and other metabolic bone diseases but, to our knowledge, it has not been evaluated in the treatment of established postmenopausal osteoporosis. OBJECTIVE: To test the efficacy and safety of daily treatment with risedronate to reduce the risk of vertebral and other fractures in postmenopausal women with established osteoporosis. DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled trial of 2458 ambulatory postmenopausal women younger than 85 years with at least 1 vertebral fracture at baseline who were enrolled at 1 of 110 centers in North America conducted between December 1993 and January 1998. INTERVENTIONS: Subjects were randomly assigned to receive oral treatment for 3 years with risedronate (2.5 or 5 mg/d) or placebo. All subjects received calcium, 1000 mg/d. Vitamin D (cholecalciferol, up to 500 IU/d) was provided if baseline levels of 25-hydroxyvitamin D were low. MAIN OUTCOME MEASURES: Incidence of new vertebral fractures as detected by quantitative and semiquantitative assessments of radiographs; incidence of radiographically confirmed nonvertebral fractures and change from baseline in bone mineral density as determined by dual x-ray absorptiometry. RESULTS: The 2.5 mg/d of risedronate arm was discontinued after 1 year; in the placebo and 5 mg/d of risedronate arms, 450 and 489 subjects, respectively, completed all 3 years of the trial. Treatment with 5 mg/d of risedronate, compared with placebo, decreased the cumulative incidence of new vertebral fractures by 41 % (95% confidence interval [CI], 18%-58%) over 3 years (11.3 % vs 16.3%; P= .003). A fracture reduction of 65% (95% CI, 38%-81 %) was observed after the first year (2.4% vs 6.4%; P<.001). The cumulative incidence of nonvertebral fractures over 3 years was reduced by 39% (95% CI, 6%-61 %) (5.2 % vs 8.4%; P = .02). Bone mineral density increased significantly compared with placebo at the lumbar spine (5.4% vs 1.1 %), femoral neck (1.6% vs -1.2%), femoral trochanter (3.3% vs -0.7%), and midshaft of the radius (0.2% vs -1.4%). Bone formed during risedronate treatment was histologically normal. The overall safety profile of risedronate, including gastrointestinal safety, was similar to that of placebo. CONCLUSIONS: These data suggest that risedronate therapy is effective and well tolerated in the treatment of women with established postmenopausal osteoporosis.

First Health Services Corporation

Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group.

Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R.
Osteoporos Int. 2000;11(1):83-91.

Centre Universitaire d'Investigation du Metabolisme Osseux et du Cartilage Articulaire, University of Liege, Belgium.

The purpose of this randomized, double-masked, placebo-controlled study was to determine the efficacy and safety of risedronate in the prevention of vertebral fractures in postmenopausal women with established osteoporosis. The study was conducted at 80 study centers in Europe and Australia. Postmenopausal women (n = 1226) with two or more prevalent vertebral fractures received risedronate 2.5 or 5 mg/day or placebo; all subjects also received elemental calcium 1000 mg/day, and up to 500 IU/day vitamin D if baseline levels were low. The study duration was 3 years; however, the 2.5 mg group was discontinued by protocol amendment after 2 years. Lateral spinal radiographs were taken annually for assessment of vertebral fractures, and bone mineral density was measured by dual-energy X-ray absorptiometry at 6-month intervals. Risedronate 5 mg reduced the risk of new vertebral fractures by 49% over 3 years compared with control ($p<0.001$). A significant reduction of 61% was seen within the first year ($p = 0.001$). The fracture reduction with risedronate 2.5 mg was similar to that in the 5 mg group over 2 years. The risk of nonvertebral fractures was reduced by 33% compared with control over 3 years ($p = 0.06$). Risedronate significantly increased bone mineral density at the spine and hip within 6 months. The adverse-event profile of risedronate, including gastrointestinal adverse events, was similar to that of control. Risedronate 5 mg provides effective and well-tolerated therapy for severe postmenopausal osteoporosis, reducing the incidence of vertebral fractures and improving bone density in women with established disease.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

First Health Services Corporation

Alendronate and risedronate: what you need to know about their upper gastrointestinal tract toxicity.

Baker DE.

Rev Gastroenterol Disord. 2002;2(1):20-33.
College of Pharmacy, Washington State University, Spokane, WA, USA.

Adverse upper gastrointestinal (GI) tract events can occur with alendronate or risedronate therapy. Although the short-term, non-placebo-controlled comparisons of alendronate and risedronate indicated that risedronate therapy may be associated with a lower risk of upper GI toxicity than alendronate therapy, the placebo-controlled comparison shows no difference in the risk of upper GI toxicity between the two drugs. The risk of an adverse upper GI event increases when these drugs are used concurrently with nonsteroidal anti-inflammatory drug (NSAID) therapy, but this incidence is no more than that observed with concurrent placebo and NSAID therapy. Also, the risk of these adverse GI tract events can be decreased by following the dosing instructions (e.g., avoid lying down for 30 minutes after taking the drug and take the drug with a full glass of water) and may be decreased with once-weekly dosing.

Publication Types:

- Review
- Review, Tutorial

First Health Services Corporation

Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials.

Taggart H, Bolognese MA, Lindsay R, Ettinger MP, Mulder H, Josse RG, Roberts A, Zippel H, Adami S, Ernst TF, Stevens KP. Mayo Clin Proc. 2002 Mar;77(3):262-70.

Sponsored by Procter and Gamble

Department of Health Care for the Elderly, Belfast City Hospital, Belfast, Northern Ireland, United Kingdom. hugh.taggart@bch.n-i.nhs.uk

Risedronate sodium is a pyridinyl bisphosphonate effective for treatment and prevention of postmenopausal and glucocorticoid-induced osteoporosis. Some bisphosphonates have been associated with upper gastrointestinal (GI) tract adverse effects. The objective of this study was to determine the frequency of upper GI tract adverse events associated with risedronate, especially among high-risk patients. The GI tract adverse events reported during 9 multicenter, randomized, double-blind, placebo-controlled studies of risedronate conducted from November 1993 to April 1998 were pooled and evaluated. The evaluation included 10,068 men and women who received placebo (n=5048) or 5 mg of risedronate sodium (n=5020) for up to 3 years (intent-to-treat population). Studies incorporated a comprehensive, prospective evaluation of GI tract adverse events. Adverse event information was collected every 3 months. The treatment groups were similar with respect to baseline GI tract disease and use of concomitant treatments during the studies. At study entry, 61.0% of patients had a history of GI tract disease and 38.7% had active GI tract disease; 20.5% used antisecretory drugs during the studies. Sixty-three percent used aspirin and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the studies. Upper GI tract adverse events were reported by 29.6% of patients in the placebo group compared with 29.8% in the risedronate group. The risk of experiencing such an event in the risedronate group was 1.01 (95% confidence interval, 0.94-1.09) relative to the placebo group (P=.77). The rate of upper GI tract adverse events per 100 patient-years was 19.2 in the placebo group compared with 20.0 in the risedronate group (P=.30). Risedronate-treated patients with active heartburn, esophagitis, other esophageal disorders, or peptic ulcer disease at study entry did not experience worsening of their underlying conditions or an increased frequency of upper GI tract adverse events overall. Concomitant use of NSAIDs, requirement for gastric antisecretory drugs, or the presence of active GI tract disease did not result in a higher frequency of upper GI tract adverse events in the risedronate-treated patients compared with controls. Endoscopy, performed in 349 patients, demonstrated no statistically significant differences across treatment groups. The results of this extensive evaluation indicate that daily treatment with 5 mg of risedronate sodium is not associated with an increased frequency of adverse GI tract effects, even among patients at high risk for these events.

Publication Types:

- Meta-Analysis

First Health Services Corporation

Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women.

Lanza FL, Hunt RH, Thomson AB, Provenza JM, Blank MA.
Gastroenterology. 2000 Sep;119(3):631-8.

Supported by **Merck Research** Laboratories
Houston Institute for Clinical Research, Houston, Texas 77074, USA. dr.lanza@pdq.net

BACKGROUND & AIMS: Bisphosphonates are effective treatment for osteoporosis, but upper gastrointestinal injury associated with some compounds has caused concern. This study compared the incidence of gastric ulcers after treatment with risedronate, a pyridinyl bisphosphonate, and alendronate, a primary amino bisphosphonate. Esophageal and gastroduodenal injury assessed by endoscopy scores was a secondary endpoint. METHODS: Healthy, postmenopausal women (n = 515) received 5 mg risedronate (n = 255) or 10 mg alendronate (n = 260) for 2 weeks. At baseline and on days 8 and 15, subjects underwent endoscopy and evaluator-blinded assessment of the esophageal, gastric, and duodenal mucosa. RESULTS: Gastric ulcers were observed during the treatment period in 9 of 221 (4.1%) evaluable subjects in the risedronate group compared with 30 of 227 (13.2%) in the alendronate group ($P < 0.001$). Mean gastric endoscopy scores for the risedronate group were lower than those for the alendronate group at days 8 and 15 ($P <= 0.001$). Mean esophageal and duodenal endoscopy scores were similar in the 2 groups at days 8 and 15. Esophageal ulcers were noted in 3 evaluable subjects in the alendronate group, compared with none in the risedronate group, and duodenal ulcers were noted in 1 evaluable subject in the alendronate group and 2 in the risedronate group. CONCLUSIONS: At doses used for the treatment of osteoporosis, risedronate was associated with a significantly lower incidence of gastric ulcers than alendronate. These findings confirm that bisphosphonates differ in their potential to damage the gastroesophageal mucosa.

First Health Services Corporation

Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group.

McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY; Hip Intervention Program Study Group.

N Engl J Med. 2001 Feb 1;344(5):333-40.
Oregon Osteoporosis Center and Providence Medical Center, Portland 97213, USA.
mmcclung@oregonosteoporosis.com

BACKGROUND: Risedronate increases bone mineral density in elderly women, but whether it prevents hip fracture is not known. METHODS: We studied 5445 women 70 to 79 years old who had osteoporosis (indicated by a T score for bone mineral density at the femoral neck that was more than 4 SD below the mean peak value in young adults [-4] or lower than -3 plus a nonskeletal risk factor for hip fracture, such as poor gait or a propensity to fall) and 3886 women at least 80 years old who had at least one nonskeletal risk factor for hip fracture or low bone mineral density at the femoral neck (T score, lower than -4 or lower than -3 plus a hip-axis length of 11.1 cm or greater). The women were randomly assigned to receive treatment with oral risedronate (2.5 or 5.0 mg daily) or placebo for three years. The primary end point was the occurrence of hip fracture. RESULTS: Overall, the incidence of hip fracture among all the women assigned to risedronate was 2.8 percent, as compared with 3.9 percent among those assigned to placebo (relative risk, 0.7; 95 percent confidence interval, 0.6 to 0.9; P=0.02). In the group of women with osteoporosis (those 70 to 79 years old), the incidence of hip fracture among those assigned to risedronate was 1.9 percent, as compared with 3.2 percent among those assigned to placebo (relative risk, 0.6; 95 percent confidence interval, 0.4 to 0.9; P=0.009). In the group of women selected primarily on the basis of nonskeletal risk factors (those at least 80 years of age), the incidence of hip fracture was 4.2 percent among those assigned to risedronate and 5.1 percent among those assigned to placebo (P=0.35). CONCLUSIONS: Risedronate significantly reduces the risk of hip fracture among elderly women with confirmed osteoporosis but not among elderly women selected primarily on the basis of risk factors other than low bone mineral density.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

First Health Services Corporation

Risedronate reduces the risk of first vertebral fracture in osteoporotic women.

Heaney RP, Zizic TM, Fogelman I, Olszynski WP, Geusens P, Kasibhatla C, Alsayed N, Isaia G, Davie MW, Chesnut CH 3rd.

Osteoporos Int. 2002;13(6):501-5.
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Risedronate treatment reduces the risk of vertebral fracture in women with existing vertebral fractures, but its efficacy in prevention of the first vertebral fracture in women with osteoporosis but without vertebral fractures has not been determined. We examined the risk of first vertebral fracture in postmenopausal women who were enrolled in four placebo-controlled clinical trials of risedronate and who had low lumbar spine bone mineral density (BMD) (mean T-score = -3.3) and no vertebral fractures at baseline. Subjects received risedronate 5 mg (n = 328) or placebo (n = 312) daily for up to 3 years; all subjects were given calcium (1000 mg daily), as well as vitamin D supplementation (up to 500 IU daily) if baseline serum 25-hydroxyvitamin D levels were low. The incidence of first vertebral fracture was 9.4% in the women treated with placebo and 2.6% in those treated with risedronate 5 mg (risk reduction of 75%, 95% confidence interval 37% to 90%; P = 0.002). The number of patients who would need to be treated to prevent one new vertebral fracture is 15. When subjects were stratified by age, similar significant reductions were observed in patients with a mean age of 64 years (risk reduction of 70%, 95% CI 8% to 90%; P = 0.030) and in those with a mean age of 76 years (risk reduction of 80%, 95% CI 7% to 96%; P = 0.024). Risedronate treatment therefore significantly reduces the risk of first vertebral fracture in postmenopausal women with osteoporosis, with a similar magnitude of effect early and late after the menopause.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

First Health Services Corporation

Risedronate prevents new vertebral fractures in postmenopausal women at high risk.

Watts NB, Josse RG, Hamdy RC, Hughes RA, Manhart MD, Barton I, Calligeros D, Felsenberg D.

J Clin Endocrinol Metab. 2003 Feb;88(2):538-41.
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Independent risk factors for fracture include advanced age, preexisting fractures, and low bone mineral density. Rised-ronate has been shown in several large trials to be safe and effective for patients with osteoporosis, but its effects in populations at high risk are not well characterized. To determine the effect of risedronate on vertebral fracture in high-risk subjects, we pooled data from two randomized, double-blind studies [Vertebral Efficacy with Risedronate Therapy (VERT) Multinational (VERT-MN) and VERT-North America (VERT-NA)] in 3684 postmenopausal osteoporotic women treated with placebo or risedronate 2.5 or 5 mg/d and analyzed fracture risk in subgroups of subjects at high risk for fracture due to greater age or more prevalent fractures (vs. median for overall study population), or lower bone mineral density (T-score, -2.5 or less). Fractures were diagnosed by quantitative and semiquantitative assessment of radiographs at baseline and 1 yr. In the overall population, treatment for 1 yr with risedronate 5 mg/d reduced the risk of new vertebral fractures by 62% vs. control (relative risk, 0.38; 95% confidence interval, 0.25, 0.56; $P < 0.001$) and of multiple new vertebral fractures by 90% vs. control (relative risk, 0.10; 95% confidence interval, 0.04, 0.26; $P < 0.001$). Consistent risk reductions were observed at 1 yr in the risedronate-treated high-risk subgroups. Significant reduction in fracture risk after 1 yr is an important benefit in patients at high risk for fracture because, without treatment, these patients are likely to sustain new fractures in the near term.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

First Health Services Corporation

The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis.

Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, Garnero P, Bouxsein ML, Bilezikian JP, Rosen CJ; PaTH Study Investigators.
N Engl J Med. 2003 Sep 25;349(13):1207-15. Epub 2003 Sep 20.

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BACKGROUND: Parathyroid hormone increases bone strength primarily by stimulating bone formation, whereas antiresorptive drugs reduce bone resorption. We conducted a randomized, double-blind clinical study of parathyroid hormone and alendronate to test the hypothesis that the concurrent administration of the two agents would increase bone density more than the use of either one alone. METHODS: A total of 238 postmenopausal women (who were not using bisphosphonates) with low bone mineral density at the hip or spine (a T score of less than -2.5, or a T score of less than -2.0 with an additional risk factor for osteoporosis) were randomly assigned to daily treatment with parathyroid hormone (1-84) (100 microg; 119 women), alendronate (10 mg; 60 women), or both (59 women) and were followed for 12 months. Bone mineral density at the spine and hip was assessed by dual-energy x-ray absorptiometry and quantitative computed tomography. Markers of bone turnover were measured in fasting blood samples. RESULTS: The bone mineral density at the spine increased in all the treatment groups, and there was no significant difference in the increase between the parathyroid hormone group and the combination-therapy group. The volumetric density of the trabecular bone at the spine increased substantially in all groups, but the increase in the parathyroid hormone group was about twice that found in either of the other groups. Bone formation increased markedly in the parathyroid hormone group but not in the combination-therapy group. Bone resorption decreased in the combination-therapy group and the alendronate group. CONCLUSIONS: There was no evidence of synergy between parathyroid hormone and alendronate. Changes in the volumetric density of trabecular bone, the cortical volume at the hip, and levels of markers of bone turnover suggest that the concurrent use of alendronate may reduce the anabolic effects of parathyroid hormone. Longer-term studies of fractures are needed to determine whether and how antiresorptive drugs can be optimally used in conjunction with parathyroid hormone therapy.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

First Health Services Corporation

NSAID Comparison Chart

Class / Agent	Generic Available	Usual Dosage Range	Max /day
Acetic Acids			
Indomethacin (Indocin®)	YES	25-50mg TID	200 mg
Indomethacin SR	YES	75 mg QD - BID	150 mg
Sulindac (Clinoril®)	YES	150-200mg BID	400 mg
Tolmetin (Tolectin®)	YES	200-600mg TID-QID	1800 mg
Diclofenac (Voltaren®)	YES	25-50mg BID-TID	225 mg
Diclofenac potassium (Cataflam®)	YES	50 mg TID, 75 mg BID	200 mg
Diclofenac+Misoprostol (Arthrotec®)	**NO**	1 tab BID-QID	225 mg
Ketorolac (Toradol®)	YES	10mg po q4-6h	40mg
Ketorolac injection	YES	15-30mg **IM** q4-6h	120mg
Etodolac (Lodine®)	YES	400-600mg BID	1200 mg
Propionic Acids			
Fenoprofen (Nalfon®)	YES	300-600mg TID-QID	3200 mg
Flurbiprofen (Ansaid®)	YES	50-100mg TID-QID	300 mg
Ibuprofen (Motrin®)	YES	200-600mg TID-QID	3200 mg
Ketoprofen (Orudis®)		25-100mg TID-QID	300 mg
Naproxen (Naprosyn®)	YES	125-500mg BID	1500 mg
Naproxen sodium (Anaprox®)	YES	250-500 mg BID	1375 mg
Oxaprozin (DayPro®)	YES	600-1800mg QD	1800 mg
Oxicams			
Piroxicam (Feldene®)	YES	10-20mg QD	20 mg
Meloxicam (Mobic®)	**NO**	20-40mg QD	15 mg
Naphthylalkanones			
Nabumetone (Relafen®) ☎	YES	1-2g QD	2000 mg
Fenamates (Anthranilic Acids)			
Meclofenamate (Meclomen®)	YES	50 mg Q4-6h	400 mg
Mefenamic Acid (Ponstel®)	**NO**	250 mg QID	1000 mg

Most NSAIDs are available generically. Exceptions are the Selective COX2 Inhibitors (previously reviewed by the P&T Committee) Mobic®, Ponstel®, and Arthrotec®. Therefore the following review will focus on the three "brand only" traditional NSAIDs.

First Health Services Corporation

Characteristic	Arthrotec® (diclofenac sodium/misoprostol)	Ponstel® (mefenamic acid)	Mobic® (meloxicam)
Pharmacology	Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit anti-inflammatory, analgesic, and antipyretic properties. Their mechanism of action is thought to be related to prostaglandin synthetase (cyclooxygenase) inhibition. Misoprostol is a synthetic prostaglandin E1 analog with gastric antisecretory and mucosal protective properties		
Manufacturer	Pharmacia	Parke-Davis	
Date of FDA approval	December 24, 1997	January 1, 1982	April 4, 2000
Generic available?	No (separate ingredients are available as generic)	No	No
Dosage forms / route of admin	Tablets 50 mg diclofenac/200 mcg misoprostol 75 mg diclofenac/200 mcg misoprostol	250 mg oral capsules	7.5 mg and 15 mg oral capsules
Dosing frequency	2-4 times a day	4 times a day	Once daily
General Dosing guidelines	• Max dose of misoprostol = 800 mcg/day • Osteoarthritis: 50 mg BID- TID or 75 mg BID • Max dose of diclofenac = 150 mg/day • Rheumatoid Arthritis: 50 mg BID-QID or 75 mg BID • Max dose of diclofenac = 225 mg/day	• For acute pain in adults and adolescents = 14 years of age, 500 mg as initial dose followed by 250 mg every 6 hours as needed (usually not to exceed one week) with food. • For primary dysmenorrhea, 500 mg as an initial dose followed by 250 mg every 6 hours with food, starting with the onset of bleeding and associated symptoms. Treatment should not be necessary for more than 2 to 3 days.	• Starting and maintenance dose is 7.5 mg once daily. • Maximum dose is 15 mg per day. • May be taken without regard to timing of meals.
Pediatric Labeling	Safety and effectiveness in pediatric patients have not been established.	Age 14 and up	Safety and effectiveness in patients under 18 years of age have not been established.
FDA Labeled Indications	Treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications.	• Relief of mild to moderate pain in patients = 14 years of age when therapy will not exceed one week. • Treatment of primary dysmenorrhea.	Relief of signs and symptoms of osteoarthritis.
Other studied uses	ankylosing spondylitis, tendonitis, dental	Menorrhagia, low back pain, osteoarthritis,	Rheumatoid arthritis, low back pain, sciatica

First Health Services Corporation

Characteristic	Arthrotec® (diclofenac sodium/misoprostol)	Ponstel® (mefenamic acid)	Mobic® (meloxicam)
	pain	rheumatoid arthritis	
Contraindications	• Hypersensitivity to diclofenac, misoprostol, or other prostaglandins. • Do not use in patients who have experienced asthma, urticaria, or other allergic-type response after taking aspirin or other NSAID.	• Hypersensitivity to mefenamic acid. • Do not use in patients who have experienced asthma, urticaria, or other allergic-type response after taking aspirin or other NSAID.	• Hypersensitivity to meloxicam. • Do not use in patients who have experienced asthma, urticaria, or other allergic-type response after taking aspirin or other NSAID.
Drug interactions	?Aspirin, digoxin, antihypertensive medications, lithium, diuretics, cholestyramine	Aspirin, antihypertensive medications, lithium, diuretics, cholestyramine, antacids (magnesium hydroxide ?Cmax & AUC).	Aspirin, antihypertensive medications, lithium, diuretics, cholestyramine,
Major Adverse Events &Warnings	• GI ulcerations • GI upset • Hypertension • Abdominal pain • Diarrhea • Renal function impairment (increased risk with dehydration) • Anaphylactoid reactions • Elevations in hepatic enzymes • Anemia • Aseptic meningitis • Fluid retention and edema • Avoid use in patients with porphyria • Avoid use in patients with aspirin-sensitive asthma • Increased risk of bleeding with concomitant warfarin use • May increase levels of cyclosporine and methotrexate • Not recommend for use in nursing mothers • Pregnancy: Category X: Because of its	• GI ulcerations • GI upset • Hypertension • Abdominal pain • Diarrhea • Flatulence • Renal function impairment (increased risk with dehydration • Anaphylactoid reactions • Elevations in hepatic enzymes • Anemia • Aseptic meningitis • Fluid retention and edema • Avoid use in patients with aspirin-sensitive asthma • Increased risk of bleeding with concomitant warfarin use • May increase levels of cyclosporine and methotrexate • Increased bleeding time • Not recommend for use in nursing mothers • Pregnancy: Category C	• GI ulcerations • Nausea • Abdominal pain • Diarrhea • Flatulence • Renal function impairment (increased risk with dehydration • Anaphylactoid reactions • Elevations in hepatic enzymes Increased bleeding time • Anemia • Aseptic meningitis • Rash • Headache • Avoid use in patients with aspirin-sensitive asthma • Increased risk of bleeding with concomitant warfarin use • Not recommend for use in nursing mothers • Pregnancy: Category C • In late pregnancy can cause premature closure of the ductus arteriosus

First Health Services Corporation

Characteristic	Arthrotec® (diclofenac sodium/misoprostol)	Ponstel® (mefenamic acid)	Mobic® (meloxicam)
	abortifacient property, misoprostol is contraindicated in pregnant women	• In late pregnancy can cause premature closure of the ductus arteriosus	
Pharmacokinetics issues	• Rate and extent of absorption of both diclofenac and misoprostol from Arthrotec 50 and Arthrotec 75 are similar to those from diclofenac and misoprostol formulations administered alone. • No differences detected in the pharmacokinetics of diclofenac in patients with renal or hepatic impairment. • Plasma concentrations decline biexponentially, the terminal phase half-life is 2 hours. The major metabolites have shorter half-lives than the parent compound. • Patients with renal impairment exhibited a doubling of half-life, Cmax, and AUC of misoprostol. • Elderly – no differences in diclofenac pharmacokinetics, the AUC for misoprostol is increased in the elderly	• Pharmacokinetics parameters have not been studied in patients with renal insufficiency. The manufacturer does not recommend use in patients with pre-existing renal disease or patients with significantly impaired renal function. • Half-life of parent compound = 2 hours. There are two primary metabolites, but the activity and the half-life of these compounds have not been determined. • Pharmacokinetic parameters have not been studied in patients with hepatic disease. Patients with acute or chronic hepatic disease may require reduced doses (hepatic metabolism is a significant elimination pathway for mefenamic acid).	• No change in pharmacokinetic parameters when administered with antacids • Half-life = 15 – 20 hours • Significant biliary and/or enteral secretion • Gender – young females exhibit slightly lower concentration than young males • Elderly males – similar pharmacokinetics to young males • Elderly females – higher AUC and Cmax compared to young females (= 55 years of age). The adverse effect profile was comparable for both of the elderly populations. • Mild and moderate hepatic impairment – no significant difference in plasma concentrations (patients with severe hepatic impairment have not been adequately studied). • Not dialyzable
Dosage adjustment in key populations	Elderly • No dosage adjustment necessary in the elderly for pharmacokinetic reasons. • No significant differences in the safety profile in the elderly.	• Pharmacokinetic differences due to race have not been identified. • Caution should be used in treating the elderly (65 years and older).	• No need for dosage adjustment in patients with mild to moderate renal impairment (CrCL > 15 ml/min). Use in severe renal impairment is not recommended. • Caution should be used in treating the elderly (65 years and older).
Place in therapy	• For gastric ulcer prevention, the 200 mcg QID and TID regimens are therapeutically equivalent, but more protective than the BID regimen. • For duodenal ulcer prevention, the QID regimen is more protective than the TID	• Naproxen, ibuprofen and diclofenac are the most studied NSAIDs due to the large CLASS and VIGOR trials comparing these agents to Celebrex® and Vioxx®. These trials found fewer ulcers in the COX-2 patients, but more serious adverse effects in the COX-2 patients. Longer half-life, enterohepatic recirculation, lack of COX-2 specificity, acidity and dose contribute to GI toxicity of the NSAIDs. Flurbiprofen, ketoprofen, fenoprofen, tolmetin, aspirin, oxaprozin, naproxen indomethacin, ibuprofen and ketorolac demonstrate a higher affinity for COX-1. Piroxicam, nabumetone, etodolac, meloxicam	

First Health Services Corporation

Characteristic	Arthrotec® (diclofenac sodium/misoprostol)	Ponstel® (mefenamic acid)	Mobic® (meloxicam)
	or BID regimens. • The QID regimen is less well tolerated because of the usually self-limited diarrhea related to the misoprostol dose.	and diclofenac demonstrate a higher affinity for COX-2. • NSAIDs are equally efficacious in head-to-head trials. There is interpatient variability in response to individual NSAIDs.	

Semin Arthritis Rheum. 1997 Apr;26(5):755-70.

A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology.

Towheed TE, Hochberg MC.

Department of Medicine, University of Maryland School of Medicine, Baltimore, USA.

We systematically reviewed randomized controlled trials (RCTs) of pharmacological therapy in knee osteoarthritis (OA), published between 1966 and August 1994. RCTs were identified by MEDLINE, supplemented by a manual search of reference lists. Qualitative assessment of RCTs was performed using Gotzsche's method; design and analysis features were rated on a scale of 0 (worst) to 8 (best). Heller et al's method was used to compare efficacy of nonsteroidal antiinflammatory drugs (NSAIDs) in comparative trials. A total of 80 RCTs were analyzed (45 involved NSAIDs, 3 analgesics, 5 intraarticular [IA] steroids, 9 biological agents, including IA hyaluronic acid, and 18 mixed modalities, including topical capsaicin). The median design and analysis scores for all 80 RCTs were 2 and 5, respectively. NSAIDs were superior to placebo in all short-term trials, but in the 32 comparative NSAID trials, only five (16%) found significant differences in efficacy. Heller et al's method identified differences in 14 NSAID comparisons; etodolac (600 mg/day) was superior in five of its nine comparisons. Indomethacin and aspirin were the most toxic NSAIDs. IA steroids were superior to placebo in short-term efficacy (< 1 month). Biological agents were superior to placebo and generally well tolerated over a mean follow-up of 48 weeks. Acetaminophen was superior to placebo and was comparably efficacious to low-dose naproxen and ibuprofen (< 2,400 mg/day). The data support the use of acetaminophen, topical capsaicin, IA steroids, IA hyaluronic acid, and NSAIDs in the treatment of patients with knee OA.

Inflamm Res. 2001 Mar;50 Suppl 1:S30-4.

A comparison of the efficacy and tolerability of meloxicam and diclofenac in the treatment of patients with osteoarthritis of the lumbar spine.

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CHU Trousseau, Service de Rhumatologie, Tours, France.

OBJECTIVE: The aim of this study was to evaluate the efficacy and tolerability of meloxicam compared with diclofenac in patients with osteoarthritis of the lumbar spine. SUBJECTS: 229 patients with radiologically confirmed osteoarthritis of the lumbar spine. TREATMENT AND METHODS: Once-daily meloxicam 7.5 mg tablet or diclofenac 100 mg slow release tablet. Efficacy and tolerability parameters were assessed at baseline and after 3, 7 and 14 days of treatment. RESULTS: The two drugs had equal short-term efficacy, with pain on motion of lumbar spine significantly ($p<0.05$) decreased at Day 3. Secondary efficacy variables were also significantly improved at Days 3, 7 and 14. There were no statistically significant differences between the two drugs, although the global tolerability of meloxicam was significantly better than for diclofenac, as assessed by the investigators ($p = 0.0072$) and the patients ($p = 0.049$). CONCLUSIONS: Meloxicam and diclofenac were equivalent in relieving the acute pain associated with osteoarthritis of the lumbar spine. However, meloxicam was much better tolerated.

Clin Pharmacol Ther. 1999 May;65(5):533-44.

Comparison of inhibitory effects of meloxicam and diclofenac on human thromboxane biosynthesis after single doses and at steady state.

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OBJECTIVE: To evaluate the extent of human cyclooxygenase-1 (COX-1) inhibition by meloxicam, which has been reported to preferentially inhibit cyclooxygenase-2 (COX-2). The effects of meloxicam were compared with those of diclofenac, a nonselective COX inhibitor.

METHODS: COX-1 inhibition was determined by measuring thromboxane B2 (TXB2)-generation from clotting whole blood ex vivo after single oral doses of 7.5 and 15 mg meloxicam and 75 mg diclofenac and at steady state (15 mg meloxicam daily and 150 mg diclofenac daily). The effect was expressed as percentage inhibition of serum TXB2 generation and was directly related to the serum drug concentration with use of a standard sigmoidal E(max) model.

RESULTS: In terms of inhibition of TXB2 generation, diclofenac was about 1 order of magnitude more potent than meloxicam, indicated by a diclofenac EC50 (concentration of drug required to cause 50% of maximum effect) that was about 10 times lower than that of meloxicam (EC50 diclofenac single doses: 37.50+/-29.64; EC50 meloxicam single doses: 677.50+/-189.08). However, serum concentrations of meloxicam after administration of 15 mg were approximately 10-fold higher than those of diclofenac. Therefore there was no statistically significant difference in the area under the effect time curve ($P = .115$) and the mean effect ($P = .424$) between meloxicam and diclofenac. The EC50 of both drugs was significantly higher at steady state (diclofenac steady state: 87.07+/-55.24 ng/mL; meloxicam steady state: 1850.12+/-829.93 ng/mL) than after a single dose ($P < .001$).

CONCLUSION: These data show that meloxicam inhibits TXB2 generation at clinically relevant doses, although less potently than diclofenac. Thus our data suggest that the COX-2 preference of meloxicam observed in vitro may not result in clinical advantages when the higher dose of 15 mg is needed. Because of the increase in EC50 at steady state, COX-1 is relatively spared when the lower dose of 7.5 mg is administered.

Br J Rheumatol. 1998 Sep;37(9):937-45.

Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA Study Group. Meloxicam Large-scale International Study Safety Assessment.

Hawkey C, Kahan A, Steinbruck K, Alegre C, Baumelou E, Begaud B, Dequeker J, Isomaki H, Littlejohn G, Mau J, Papazoglou S.

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Although widely used, non-steroidal anti-inflammatory drugs (NSAIDs) are associated with a high incidence of gastrointestinal (GI) side-effects. Inhibition of the cyclooxygenase (COX) enzyme is the basis for both the efficacy and toxicity of NSAIDs. The discovery of two COX isoforms, constitutive COX-1 and inducible COX-2, has led to the hypothesis that selective inhibition of COX-2 will minimize the potential for GI toxicity without compromising efficacy. The Meloxicam Large-scale International Study Safety Assessment (MELISSA) trial reported here was therefore set up to investigate the tolerability of meloxicam, a preferential inhibitor of COX-2, compared to diclofenac. MELISSA was a large-scale, double-blind, randomized, international, prospective trial, conducted over 28 days in patients with symptomatic osteoarthritis. Patients received either meloxicam 7.5 mg or diclofenac 100 mg slow release, the recommended doses for the treatment of osteoarthritis.

Evaluation of the profile of adverse events was the main aim of the trial, together with assessment of efficacy. A total of 9323 patients received treatment (4635 and 4688 in the meloxicam and diclofenac groups, respectively). Significantly fewer adverse events were reported by patients receiving meloxicam. This was attributable to fewer GI adverse events (13%) compared to diclofenac (19%; $P < 0.001$). Of the most common GI adverse events, there was significantly less dyspepsia ($P < 0.001$), nausea and vomiting ($P < 0.05$), abdominal pain ($P < 0.001$) and diarrhoea ($P < 0.001$) with meloxicam compared to diclofenac. Five patients on meloxicam experienced a perforation, ulcer or bleed vs seven on diclofenac (not significant). No endoscopically verified ulcer complication was detected in the meloxicam group compared to four with diclofenac. There were five patient days of hospitalization in patients on meloxicam compared to 121 with diclofenac. Adverse events caused withdrawal from the study in 254 patients receiving meloxicam (5.48%) compared to 373 (7.96%) on diclofenac ($P < 0.001$). These differences were attributable to differences in reported GI adverse events (3.02% on meloxicam vs 6.14% on diclofenac; $P < 0.001$).

Differences in efficacy, as assessed by visual analogue scales, consistently favoured diclofenac. In all instances, 95% confidence intervals did not cross zero, suggesting a statistically significant effect. However, differences were small (4.5-9.01% difference) and did not reach pre-determined levels of clinical significance. Nevertheless, significantly more patients discontinued meloxicam because of lack of efficacy (80 out of 4635 vs 49 out of 4688; $P < 0.01$). The MELISSA trial confirms earlier studies suggesting that meloxicam has a significantly improved GI tolerability profile in comparison with other NSAIDs, including diclofenac. These results may in part reflect the preferential COX-2 selectivity of meloxicam, although the dose and other aspects of tolerability may be important. These results may provide support for the hypothesis that selective inhibition of COX-2 relative to COX-1 might be an effective approach towards improved NSAID therapy.

Osteoarthritis Cartilage. 1997 Jul;5(4):283-8.

A double-blind, randomized trial to compare meloxicam 15 mg with diclofenac 100 mg in the treatment of osteoarthritis of the knee.

Goei The HS, Lund B, Distel MR, Bluhmki E.

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Meloxicam is a new nonsteroidal anti-inflammatory drug (NSAID), which, in animal tests, displays a high potency for anti-inflammatory and analgesic action. The aim of this study was to investigate the efficacy and tolerability of 15 mg meloxicam in comparison with 100 mg slow-release diclofenac in patients with osteoarthritis of the knee. Two hundred and fifty-eight patients were included in the intent-to-treat analysis; these were randomized into two groups to receive either 15 mg meloxicam (N = 128) or 100 mg diclofenac (N = 130) for a period of 6 weeks. The results with respect to efficacy showed a trend in favor of meloxicam regarding pain on movement, global efficacy and paracetamol consumption, although these differences did not reach statistical significance. The most frequently-occurring adverse events in both groups were of a gastrointestinal (GI) nature. However, there was a higher incidence (26 vs 16%) of GI adverse events in the diclofenac group compared with the meloxicam group. Both drugs were well tolerated when assessed by the patients on a visual analog scale (VAS). Thus, 15 mg meloxicam is an effective and well-tolerated therapy for osteoarthritis and compares favorably with diclofenac 100 mg, a well-established treatment for this indication.

Br J Rheumatol. 1996 Apr;35 Suppl 1:39-43.

Meloxicam in osteoarthritis: a 6-month, double-blind comparison with diclofenac sodium.

Hosie J, Distel M, Bluhmki E.

Great Western Medical, Knightswood, Glasgow.

A multicentre, double-blind, randomized study was conducted in patients with osteoarthritis (OA) of the hip or knee in order to compare the efficacy and safety of the new cyclooxygenase-2 (COX-2) inhibitor, meloxicam, with diclofenac sodium, a conventional treatment for this condition. Three hundred and thirty-six patients were treated with oral meloxicam 7.5 mg once daily or diclofenac 100 mg slow release once daily for 6 months. There were no significant differences between the treatment groups with respect to overall pain, pain on movement, global efficacy or quality of life scores at the end of treatment, all of which showed good levels of improvement. Sixty-six patients were withdrawn after the start of the double-blind phase due to adverse events (n = 21, meloxicam; n = 31, diclofenac) or to lack of efficacy (seven in each group). The median of dose paracetamol taken concomitantly was statistically significantly lower in the meloxicam group than in the diclofenac group (185 vs 245 mg/day; P = 0.0123) with a comparable proportion of patients taking concomitant paracetamol therapy in both groups. Both drugs were well tolerated, although severe adverse events, treatment withdrawal and clinically significant laboratory abnormalities were more common with diclofenac than with meloxicam. Thus, meloxicam 7.5 mg is a safe and effective treatment for OA of the hip and knee which demonstrates a trend towards an improved safety profile compared with diclofenac

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Product Information: Arthrotec(R), diclofenac sodium and misoprostol. G.D. Searle & Co., Chicago, IL, Revised November.

Product Information: MOBIC (R), meloxicam. Boehringer Ingelheim Pharma, Ridgefield, CT.

Product Information: Ponstel(R), mefenamic acid, Parke Davis, Morris Plains, NJ.

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Pharmacology

Sumatriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, eletriptan, and almotriptan are selective 5-hydroxytryptamine$_1$ (5-HT$_1$ or serotonin) receptor agonists.

Serotonin 5-HT$_1$ Receptor Agonists Receptor Site Affinity			
Drug	**High**	**Weak**	**None**
Almotriptan	5-HT$_{1D}$, 5-HT$_{1B}$, 5-HT$_{1F}$	5-HT$_{1A}$, 5-HT$_7$	5-HT$_{2-4}$, 5-HT$_6$, -adrenergic, -adrenergic, adenosine(A$_1$, A$_2$), angiotensin (AT$_1$, AT$_2$), dopaminergic D$_1$ or D$_2$, endothelin (ET$_A$, ET$_B$), tachykinin receptor sites
Eletriptan	5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1F}$	5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{2B}$, 5-HT$_7$	5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_3$, 5-HT$_4$, 5-HT$_{5A}$, 5-HT$_6$, -adrenergic, and -adrenergic, dopaminergic D$_1$or D$_2$, muscarinic, or opioid receptors
Frovatriptan	5-HT$_{1B}$, 5-HT$_{1D}$	none	Benzodiazepine receptor sites
Naratriptan	5-HT$_{1D}$	none	5-HT$_{2-4}$, -adrenergic, -adrenergic, dopaminergic, muscarinic, benzodiazepine receptor sites
Rizatriptan	5-HT$_{1B}$, 5-HT$_{1D}$	5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{1F}$, 5-HT$_7$	5-HT$_2$, 5-HT$_3$, -adrenergic, -adrenergic, dopaminergic, muscarinic, benzodiazepine receptor sites
Sumatriptan	5-HT$_1$	5-HT$_{1A}$, 5-HT$_{5A}$, 5-HT$_7$	5-HT$_{2-4}$, -adrenergic, -adrenergic, dopaminergic, muscarinic, benzodiazepine receptor sites
Zolmitriptan	5-HT$_{1D}$, 5-HT$_{1B}$	5-HT$_{1A}$	5-HT$_{2-4}$, -adrenergic, -adrenergic, dopaminergic, muscarinic, histaminic receptor sites

The vascular 5-HT$_1$ receptor subtype is present on the human basilar artery and in the vasculature of isolated human dura mater. Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation or to the release of vasoactive and proinflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of the serotonin 5-HT$_1$ receptor agonists in migraine most likely can be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release, and reduced transmission in trigeminal pain pathways

Migraine Products: Triptans			
Brand Name Generic Name	Imitrex Nasal Spray® (sumatriptan)	Imitrex Tablets® (sumatriptan)	Imitrex Injection® (sumatriptan)
Manufacturer	GSK	GSK	GSK
Date of Approval	August 26, 1997	June 1, 1995	December 28, 1992
Generic formulation available?	No	No	No
Dosage forms / route of admin	Nasal Spray – 5mg and 20mg	Tablets – 25mg, 50mg or 100mg	Injection – 6mg (12mg/ml) as ▪ Imitrex STAT dose system contains 2 prefilled single dose syringe cartridges and 1 STAT dose pen ▪ Imitrex injection cartridge pack – 2 prefilled syringe cartridges for refill of the above pen ▪ Unit of use syringes – in cartons of 2 syringes ▪ 6-mg single dose vials in cartons of 5 vials
Dosing frequency	▪ Nasal Spray – 5, 10 or 20mg is administered into one nostril. May repeat once after 2 hours. Max dose 40mg/24 hours. ▪ Safety of treating more than 4 headaches in a 30-day period had not been established.	▪ Given as a 25mg, 50mg or 100mg single dose. May repeat after 2 hours. Max dose of 200mg/24 hours. ▪ Safety of treating more than 4 headaches in a 30-day period had not been established.	▪ Maximum single recommended adult dose is 6 mg injected subcutaneously. Max dose of two 6mg injections per 24 hours. ▪ The two doses need to be separated by at least 1 hour.
Indications	Indicated for the acute treatment of migraine attacks with or without aura in adults.		Indicated for the acute treatment of migraine attacks with or without aura in adults and the acute treatment of cluster headache episodes.
Contraindications	▪ Not be given to patients with history, signs, or symptoms of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes (including ischemic bowel disease), or in patients with other significant underlying cardiovascular disease. ▪ Patients with uncontrolled hypertension ▪ Concurrent administration with MAO-A- Inhibitors or use within 2 weeks of discontinuation of MAO-A- Inhibitors ▪ Do no use within 24 hours of any ergotamine-containing or ergot-type medication and 5-HT1 agonist ▪ Do not administer to patients with hemiplegic or basilar migraine ▪ Hypersensitivity to sumatriptan or any of its components ▪ Severe hepatic impairment		
Drug interactions	▪ Ergotamine containing or Ergot-type medications (dihydroergotamine or methysergide) within 24 hours of sumatriptan should be avoided ▪ MAO-A inhibitors reduce sumatriptan clearance significantly – combination is contraindicated (sumatriptan levels are nearly doubled). ▪ SSRIs		

Migraine Products: Triptans			
Brand Name Generic Name	Imitrex Nasal Spray® (sumatriptan)	Imitrex Tablets® (sumatriptan)	Imitrex Injection® (sumatriptan)
Major AEs / Warnings	▪ Cluster headache patients often possess one or more predictive risk factors for CAD ▪ It is strongly recommended that it not be given to patients in whom unrecognized vasospastic CAD is predicted by the presence of risk factors (hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiac evaluation provides sufficient clinical evidence of no disease (for these patients it is strongly recommended that the first dose be given in a physician's office). ▪ Cardiac ischemia can occur in the absence of clinical symptoms - consideration should be given to obtain an ECG immediately following the dose ▪ Patients who are intermittent long-term users and have or acquire risk factors predictive of CAD, should undergo periodic cardiovascular evaluation. ▪ Patients with cluster headache are predominantly male and over 40 years of age, which are factors for CAD. ▪ Serious cardiac events, including some that have been fatal, have occurred with Imitrex tablets and injection. ▪ Drug-associated cerebrovascular events and fatalities. ▪ Peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea. ▪ Hypertension		
Adverse Effects	▪ Neck/Throat/Jaw pressure ▪ Burning Sensation ▪ Throat discomfort ▪ Disorder/discomfort of nasal cavity/sinuses ▪ Nausea and or vomiting ▪ Bad/unusual taste ▪ Dizziness/vertigo	▪ Chest pain/tightness/pressure or heaviness ▪ Atypical sensations – paresthesia and sensation warm/cold ▪ Pain-location specific ▪ Neck/throat/jaw – pain/tightness/ pressure ▪ Vertigo ▪ Malaise/fatigue	▪ Atypical sensations – Tingling, warm/hot sensation, cold sensation etc. ▪ Dizziness ▪ Chest discomfort – Tightness and pressure ▪ Ear, nose and throat discomfort ▪ Vision alterations ▪ Abdominal discomfort and dysphasia ▪ Injection site reaction ▪ Weakness, neck pain, myalgia, muscle cramps ▪ Flushing
Pharmacokinetics issues	▪ 15% bioavailability ▪ T1/2- 2 hours ▪ Tmax – 1.5 hour	▪ 15% bioavailability ▪ T1/2 – 2 hours ▪ Tmax – 1.5 to 2.5 hours ▪ Onset – 30 to 60 minutes	▪ T1/2- 2hours ▪ Tmax – median of 10 minutes
Dosage adjustment in key populations	Hepatic disease/functional impairment has not been studied.	Hepatic disease/functional impairment – maximum single dose should in general not exceed 50mg	No statistically significant differences in the pharmacokinetics of the injections in patients with hepatic impairment.
	Elderly – use not recommended, more likely to have decreased hepatic function, they are more at risk for CAD, and blood pressure increases may be more pronounced in the elderly.		

Migraine Products: Triptans			
Brand Name Generic Name	Imitrex Nasal Spray® (sumatriptan)	Imitrex Tablets® (sumatriptan)	Imitrex Injection® (sumatriptan)
Place in therapy/Special (Unique features)	The flexibility of form, combined with the speed and potency of the injection and the speed of onset of the nasal spray (both being faster in onset than any of the oral triptans) makes sumatriptan unique from the other triptans.		

Migraine Products: Triptans			
Brand Name Generic Name	Maxalt®, Maxalt-MLT® (rizatriptan)	Zomig®, Zomig-MLT® (zolmitriptan)	Amerge® (naratriptan)
MFT	Merck	Astra-Zeneca	GSK
Date of approval	June 29, 1998	November 25, 1997	Feb. 10, 1998
Generic formulation available?	No	No	No
Dosage forms / route of admin	Tablets – 5mg & 10mg Maxalt-MLT (orally disintegrating tablet)- 5mg & 10mg	Tablets – 2.5mg & 5mg Zomig ZMT (orally disintegrating tablet) 2.5mg Zomig nasal spray	Tablets – 1mg & 2.5mg
Dosing frequency	▪ Tablets and MLT – single doses of 5mg and 10 mg ▪ May repeat dose by at least 2 hours Max dose is 30mg/24 hours ▪ Safety of treating on average, more than 4 headaches in a 30-day period has not been established	▪ Tablets and ZMT - generally start at 2.5mg tablets or lower (manually breaking the tablet in half) ▪ May repeat dose after 2 hours ▪ Max dose is 10mg / 24 hours ▪ Safety of treating an average of more than 3 headaches in a 30 day period has not been established	▪ 1 or 2.5 mg can be used. May repeat dose once after 4 hours, for a maximum dose of 5mg/24 hours ▪ The safety of treating more than 4 headaches in a 30 day period has not been established
Indications	Indicated for the acute treatment of migraine attacks with or without aura in adults		
Contraindications	▪ Should not be given to patients with ischemic heart disease (e.g. angina, history of MI, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's Variant angina, or other significant underlying cardiovascular disease. ▪ Uncontrolled hypertension. ▪ Hypersensitivity to this agent or any of its components. ▪ Do no use within 24 hours of any ergotamine-containing or ergot-type medication and 5-HT1 agonist. ▪ Do not administer to patients with hemiplegic or basilar migraine.		
	Concurrent administration with MAO-A-Inhibitors or use within 2 weeks of discontinuation of MAO-A-Inhibitors.		▪ Should not be given to patients with peripheral vascular disease (including ischemic bowel disease).

Migraine Products: Triptans			
Brand Name Generic Name	Maxalt®, Maxalt-MLT® (rizatriptan)	Zomig®, Zomig-MLT® (zolmitriptan)	Amerge® (naratriptan)
Drug interactions	▪ Propranolol and Zomig or Maxalt has been shown to increase the plasma concentration of zolmitriptan by 50% ▪ Ergotamine-containing or ergot-type drugs (dihydroergotamine and methysergide) with in 24 hours of each other ▪ MAO-A inhibitors – contraindicated ▪ Other 5-HT1B/1D within 24 hours of Amerge, Maxalt or Zomig is contraindicated ▪ SSRIs ▪ Oral contraceptives Zolmitriptan ▪ Cimetidine		
Major AEs / Warnings	▪ It is strongly recommended that it not be given to patients in who unrecognized vasospastic CAD is predicted by the presence of risk factors (hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiac evaluation provides sufficient clinical evidence of no disease. (for these patients, it is strongly recommended that the first dose be given in a physician's office). ▪ Cardiac ischemia can occur in the absence of clinical symptoms- Consideration should be given to obtain an ECG immediately following the dose. ▪ It is recommended that patients who are intermittent long-term users and who have or acquire risk factors predictive of CAD, undergo periodic cardiovascular evaluation. ▪ Drug-associated with cerebrovascular events and fatalities. ▪ Peripheral vascular ischemia and colonic ischemia with abdominal pain and blood diarrhea. ▪ Hypertension ▪ Maxalt MLT formulation - caution phenylketonuric patients. ▪ Patients with Wolff-Parkinson-White syndrome or other arrhythmia should not receive Zomig.		
Adverse Effects	▪ Parasthesia ▪ Pain and pressure sensations ▪ Nausea ▪ Dizziness, somnolence ▪ Fatigue	▪ Parasthesia and warm sensation ▪ Tightness in throat and chest ▪ Nausea ▪ Dizziness, somnolence ▪ Fatigue	▪ Parasthesia at 2.5mg dose ▪ Pain and pressure sensations – throat and neck symptoms at 2.5mg dose

Migraine Products: Triptans			
Brand Name Generic Name	Maxalt®, Maxalt-MLT® (rizatriptan)	Zomig®, Zomig-MLT® (zolmitriptan)	Amerge® (naratriptan)
Pharmacokinetics issues	▪ Bioavailability – 40% ▪ Tmax – 1 hours ▪ T1/2 – 2 hours ▪ MLT ▪ Tmax – 1.6 to 2.5 hours ▪ Mean AUC and Cmax were slightly higher in females. Tmax was similar between males and females. ▪ Pharmacokinetic data revealed no significant differences between African Americans and Caucasians.	▪ Bioavailability – 40-46% ▪ Tmax – 1.5 hours ▪ T1/2- 3 hours ▪ ZMT ▪ Tmax – 3 hours ▪ Mean plasma concentrations are up to 1.5 times higher in females than males.	▪ Bioavailability – 74% ▪ Tmax – 2 hours ▪ T1/2 – 5.5 hours ▪ The effect of race on the pharmacokinetics has not been examined. ▪ Retrospective analysis of pharmacokinetic data between Japanese and Caucasians revealed no significant differences.
Dosage adjustment in key populations	▪ Patients receiving propranolol should receive the 5mg dose, up to a max of 3 doses in a 24 hour period ▪ Moderate hepatic insufficiency and hemodialysis patients caution should be used	Hepatic impairment – generally use doses less than 2.5mg	▪ Renal impairment – contraindicated with severe renal impairment. Mild to moderate renal impairment, max daily dose should not exceed 2.5mg over a 24 hour period and a lower starting dose should be considered ▪ Hepatic impairment- contraindicated in severe hepatic impairment. Mild to moderate hepatic impairment the max daily dose should not exceed 2.5mg over a 24 h period and a lower starting dose should be considered
Special (Unique features)	▪ Has a slightly faster onset of action , is moderately lipophilic and has a greater likelihood of 2 hour pain-free and sustained pain-free response, with lower tablet consumption per attack than Axert®, Zomig® or Imitrex®.	▪ Proven ability to treat persistent headache when the first dose fails, resulting in the highest consistency of response over time, with 95% of attacks aborted at 2 hours with 1 or 2 doses of zolmitriptan over 1 year.	▪ Known as the “gentle triptan” as it has a slower onset of action and lower recurrence rate than both sumatriptan and rizatriptan, as well as a favorable adverse effect profile. It is very lipophilic and has a long half-life – (about 5-6 hours – second to Frova®) Headache response is 48% at 2 hours , but reaches 66% by 4 hours. Amerge® has been shown to be effective in preventing menstrual migraines and is helpful in patients who have early migraine recurrence or adverse effects to other triptans.

Migraine Products: Triptans		
Brand Name Generic Name	Axert® (Almotriptan)	Frova® (frovatriptan)
MFT	Pharmacia/Upjohn	Elan
Date of approval	May 7, 2001	November 8, 2001
Generic formulation available?	No	No
Dosage forms / route of admin	Tablets – 6.25mg & 12.5mg 12.5mg tended to be more effective	Tablets – 2.5mg
Dosing frequency	▪ Single doses of 6.25mg and 12.5 mg. ▪ May repeat dose by at least 2 hours, Max is two doses in 24 hours. ▪ Safety of treating on average, more than 4 headaches in a 30-day period has not been established.	▪ Single dose of 2.5mg. ▪ May repeat dose after 2 hours. ▪ Max dose is 7.5mg / 24 hours. ▪ Safety of treating an average of more than 4 headaches in a 30 day period has not been established.
Indications	Indicated for the acute treatment of migraine attacks with or without aura in adults	
Contraindications	▪ Should not be given to patients with ischemic heart disease (e.g. angina, history of MI, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's Variant angina, or other significant underlying cardiovascular disease. ▪ Should not be given to patients with uncontrolled hypertension. ▪ Hypersensitivity to this agent or any of its components. ▪ Do no use within 24 hours of any ergotamine-containing or ergot-type medication and 5-HT1 agonist. ▪ Do not administer to patients with hemiplegic or basilar migraine.	
		▪ Should not be given to patients with cerebrovascular disease (e.g., stroke, transient ischemic attacks), or peripheral vascular disease (e.g., ischemic bowel disease).
Drug interactions	▪ Inhibitors of hepatic enzyme P-450 3A4 (e.g., ritonavir, ketoconazole, fluconazole, itraconazole, erythromycin) ▪ Ergotamine-containing or ergot-type drugs (dihydroergotamine and methysergide) with in 24 hours of each other – contraindicated ▪ Other 5-HT1B/1D within 24 hours of Axert is contraindicated ▪ SSRIs	▪ Propranolol and Frova has been shown to increase the plasma concentration of frovatriptan by 30%-60%. ▪ Ergotamine-containing or ergot-type drugs (dihydroergotamine and methysergide) with in 24 hours of each other ▪ Other 5-HT1B/1D within 24 hours of Frova is contraindicated ▪ SSRIs

Migraine Products: Triptans		
Brand Name Generic Name	Axert® (Almotriptan)	Frova® (frovatriptan)
Major AEs / Warnings	▪ It is strongly recommended that it not be given to patients in who unrecognized vasospastic CAD is predicted by the presence of risk factors (hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiac evaluation provides sufficient clinical evidence of no disease (for these patients, it is strongly recommended that the first dose be given in a physician's office). ▪ Consideration should be given to obtain an ECG immediately following the dose because cardiac ischemia can occur in the absence of clinical symptoms. ▪ It is recommended that patients who are intermittent long-term users and who have or acquire risk factors predictive of CAD, undergo periodic cardiovascular evaluation. ▪ Drug associated with cerebrovascular events and fatalities. ▪ Peripheral vascular ischemia and colonic ischemia with abdominal pain and blood diarrhea. ▪ Increased blood pressure.	
Adverse Effects	▪ Paresthesia ▪ Nausea ▪ Somnolence ▪ Dry mouth	▪ Paresthesia ▪ Dizziness ▪ Dry mouth ▪ Fatigue ▪ Flushing ▪ Hot or cold sensation ▪ Chest pain
Pharmacokinetics issues	▪ Bioavailability – 69-80% ▪ Tmax – 2.5 hours ▪ T1/2 – 3.1-3.6 hours ▪ No significant differences in the pharmacokinetics have been observed between African-American and Caucasians. ▪ Gender - no significant differences	▪ Bioavailability – 20-30% ▪ Tmax – 2-4 hours ▪ T1/2- 26 hours ▪ Gender – no differences in terminal half-life. Bioavailability and systemic exposure to frovatriptan was approximately 2 times higher in females. ▪ The effect of race on pharmacokinetics of frovatriptan has not been determined.
Dosage adjustment in key populations	▪ Renal impairment – clearance is decreased in patients with moderate renal impairment. Use with caution; dosage adjustment recommended. ▪ Hepatic impairment – no clinical trials in patients with hepatic impairment. Use with caution; dosage adjustment recommended.	▪ Hepatic impairment – no dosage adjustment necessary when given to patients with mild to moderate impairment. No clinical data in patients with severe impairment.

Migraine Products: Triptans		
Brand Name Generic Name	Axert® (Almotriptan)	Frova® (frovatriptan)
Special (Unique features)	▪ Its 2 –hour headache response is 57%-65%, similar to sumatriptan tablets, and its recurrence rate was identical to that of sumatriptan in direct comparison trials. It was shown to have a more favorable adverse event profile in these trials over sumatriptan.	▪ It has a slower onset of action, similar to naratriptan, with a 2-hour response rate of 36-46% but 60% at 4 hours. It may be a better triptan, to be used in patients with slow-onset attacks, menstrual migraine or preventively in some patients with chronic daily migraine. The extremely long half-life of this triptan makes for a better agent in these subsets of patients.

Migraine Products: Triptans	
Brand Name Generic Name	Relpax® Eletriptan
MFT	Pfizer
Date of Approval	December 26, 2002
Generic formulation available?	No
Dosage forms / route of admin	20mg and 40mg tablets
Dosing frequency	▪ Individualize dose. Single doses of 20 and 40 mg were effective for the acute treatment of migraine in adults, with a greater proportion of patients having a response following a 40 mg dose. Individuals may vary in response to doses of eletriptan tablets. An 80 mg dose, although also effective, was associated with an increased incidence of adverse events. Therefore, the maximum recommended single dose is 40 mg. If, after the initial dose, the headache improves but then returns, a repeat dose may be beneficial. If a second dose is required, it should be taken at least 2 hours after the initial dose. If the initial dose is ineffective, controlled clinical trials have not shown the second dose to be beneficial in treating the same attack. The maximum daily dose should not exceed 80mg. The safety of treating an average of more than 3 headaches in a 30-day period has not been established
Indications	▪ For acute treatment of migraine with or without aura in adults. ▪ Not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of eletriptan have not been established for cluster headache, which is present in an older, predominantly male population.
Contraindications	▪ Relpax® should not be given to patients with ischemic heart disease (e.g. angina pectoris, history of myocardial infarction, or documented silent ischemia) or patients who have symptoms, or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina or other significant underlying cardiovascular disease.
Drug interactions	▪ CYP3A4 inhibitors: Eletriptan is metabolized by the CYP3A4 enzyme. Do not use eletriptan within at least 72 hours of treatment with the following potent CYP3A4 inhibitors:Ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir. Do not use eletriptan within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect.. ▪ Should not be given within 24 hours of treatment with another 5-HT_1 agonist, and ergotamine-containing or ergot-type medication such as dihydroergotamine (DHE) or methysergide. ▪ No expected drug interactions with MAOIs
Major AEs / Warnings	▪ Relpax® should not be given to patients with cerebrovascular syndromes including (but not limited to) strokes of any type as well as transient ischemic attacks, patients with peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension, patients with known hypersensitivity or hepatic impairment. ▪ Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists.

Migraine Products: Triptans	
Brand Name Generic Name	Relpax® Eletriptan
Adverse Effects	▪ Paresthesia ▪ Nausea ▪ Dizziness ▪ Somnolence
Pharmacokinetics issues	▪ Bioavailability: 50% ▪ Tmax- 2.0 hours ▪ T1/2 : 4.4 hours ▪ Pharmacokinetics are unaffected by gender. ▪ Per manufacturer, population pharmacokinetic analysis of two clinical studies indicates no evidence of pharmacokinetic differences between Caucasians and non-Caucasians.
Dosage adjustment in key populations	▪ Do not give eletriptan to patients with severe hepatic impairment because the effect of severe hepatic impairment on eletriptan metabolism was not evaluated. No dose adjustment is necessary in mild to moderate impairment.
Special (Unique features)	The most lipophilic triptan that is metabolized mainly by cytochrome P-3A4 such that dosage adjustments are necessary or dosage is contra-indicated when administered with cytochrome P-3A4 medications, such as macrolide antibiotics and antifungals. Drug interactions hinder utilization in many cases.

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Migraine headache recurrence: relationship to clinical, pharmacological, and pharmacokinetic properties of triptans.

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BACKGROUND AND OBJECTIVES: Triptan use is associated with headache recurrence, and this has been cited as an important reason for patient dissatisfaction with the treatment. The mechanism by which recurrence occurs is not clear, and the incidence of recurrence varies with the triptan used. In order to explore the pharmacological and physiological interaction of triptans and migraine headache recurrence further, some specific clinical, pharmacological, and pharmacokinetic factors that might influence migraine recurrence were evaluated in a review of the major efficacy data for the drugs in the triptan class. These factors were 5-HT1B and 5-HT1D receptor activities, the pharmacokinetic elimination half-life of each triptan, and the clinical efficacy of each compound, determined by the proportion of patients with headache relief and the therapeutic gain over placebo. METHODS: Clinical data were derived from 31 triptan, placebo-controlled, major efficacy studies used in a previous meta-analysis. The mean recurrence rate, mean headache response, and therapeutic gain were calculated using the results from the individual clinical studies. Mean headache response and therapeutic gain were calculated at the time point used to define recurrence in each study. Data for binding affinity and potency were taken from a direct-comparison in vitro pharmacology study, and the elimination half-life quoted in the data sheet for each triptan was used. Rank correlation with recurrence rate was performed for each of the test parameters. RESULTS: Mean headache recurrence rates ranged from 17% for frovatriptan 2.5 mg to 40% for rizatriptan. Elimination half-life and recurrence were inversely correlated ($r = -1.0$, $P = .0016$). There was also a significant inverse correlation between 5-HT1B receptor potency and recurrence ($r = -0.68$, $P = .034$), but 5-HT1D receptor potency was not correlated with recurrence ($r = -0.20$, $P = .54$). In addition, the binding affinities for the 5-HT1B and 5-HT1D receptors were not correlated to headache recurrence. Importantly, it also was demonstrated that initial clinical efficacy was not correlated to headache recurrence. The correlation coefficient for headache response was 0.18 ($P = .53$) and for therapeutic gain, -0.11 ($P = .71$). CONCLUSION: The incidence of migraine headache recurrence varies between drugs in the triptan class. Migraine recurrence does not appear to be related to initial clinical efficacy, but is influenced by the pharmacological and pharmacokinetic properties of the individual triptans. The triptans with longer half-lives and greater 5-HT1B receptor potency had the lowest rates of headache recurrence.

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Economic comparison of oral triptans for management of acute migraine: implications for managed care.

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Sound, informed decision making regarding which drugs to include on a formulary should be based on the best available evidence of their clinical efficacy and incidence of adverse events. Comparative drug costs and clinical effectiveness should also be considered during the formulary development process. Clinical trials traditionally evaluate efficacy and adverse events independently, whereas effectiveness in real-life conditions is defined as some combination of efficacy and side effects. When evaluating similar medications, head-to-head efficacy and effectiveness studies are preferred. For oral triptans (serotonin 5-HT(1B,1D) receptor agonists), there are many placebo-controlled trials and several active trials that compare newer oral triptans with sumatriptan; however, there have been few comparisons of triptans in head-to-head trials. Meta-analysis is an appropriate method to evaluate multiple clinical trials critically and combine the results. A recently published meta-analysis used patient-level data to assess efficacy and adverse events across multiple triptan clinical trials. In this analysis, we combined those results with medication costs to assess the overall value among oral triptans. Using this combined approach, almotriptan was found to have the greatest economic value. It delivers comparable efficacy, placebo-like tolerability, and the highest value when compared with other triptans currently marketed in the United States.

Neurology. 2001 Oct 23;57(8):1377-83.

Comparison of rizatriptan and other triptans on stringent measures of efficacy.

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OBJECTIVE: To compare the efficacy of oral rizatriptan 10 mg with oral doses of sumatriptan, naratriptan, and zolmitriptan on stringent outcome measures. METHODS: Retrospective analysis of data from five randomized, placebo-controlled, double-masked clinical trials in which oral rizatriptan was directly compared with oral sumatriptan 100 mg (n = 772), 50 mg (n = 1116), 25 mg (n = 1183), naratriptan 2.5 mg (n = 413), and zolmitriptan 2.5 mg (n = 580) for the acute treatment of a moderate or severe migraine attack. OUTCOME MEASURES: Percentage of patients pain-free at 2 hours, symptom-free at 2 hours (no pain, nausea, photophobia, phonophobia, vomiting, or functional disability), 24-hour sustained pain-free (no headache at 2 hours, no recurrence, and no additional antimigraine medications for 24 hours). RESULTS: More patients taking rizatriptan 10 mg were pain-free at 2 hours than were patients taking sumatriptan 100 mg (40% vs 33%, $p = 0.019$), sumatriptan 50 mg (40% vs 35%, $p = 0.009$), sumatriptan 25 mg (38% vs 27%, $p < 0.001$), naratriptan 2.5 mg (45% vs 21%, $p < 0.001$), and zolmitriptan 2.5 mg (43% vs 36%, $p = 0.041$). More patients taking rizatriptan 10 mg were symptom-free at 2 hours than were patients taking sumatriptan 100 mg (31% vs 22%, $p = 0.002$), sumatriptan 50 mg (33% vs 28%, $p = 0.003$), sumatriptan 25 mg (33% vs 24%, $p < 0.001$), naratriptan 2.5 mg (30% vs 11%, $p < 0.001$), and zolmitriptan 2.5 mg (31% vs 24%, $p = 0.042$). More patients taking rizatriptan 10 mg had a 24-hour sustained pain-free response than did patients taking sumatriptan 100 mg (27% vs 23%, $p = 0.112$), sumatriptan 50 mg (30% vs 26%, $p = 0.015$), sumatriptan 25 mg (27% vs 20%, $p = 0.005$), naratriptan 2.5 mg (29% vs 17%, $p = 0.004$), and zolmitriptan 2.5 mg (32% vs 24%, $p = 0.013$). CONCLUSION: Oral rizatriptan 10 mg was more effective than oral sumatriptan, naratriptan, and zolmitriptan on stringent outcome measures of pain-free response at 2 hours, symptom-free response at 2 hours, and 24-hour sustained pain-free response.

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Comparison of triptan tablet consumption per attack: a prospective study of migraineurs in Spain.

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OBJECTIVES: To compare patient self-reported tablet consumption of rizatriptan 10 mg per attack (24 hours) with that of sumatriptan 50 mg, zolmitriptan 2.5 mg, and naratriptan 2.5 mg on an unselected, prescription-based, Spanish migraine population. METHODS: One hundred twenty community pharmacies recruited patients with migraine, who used their pharmacies, to fill a triptan prescription. In diaries, patients recorded baseline pain intensity and the number of triptan tablets and additional medication taken per attack. Patients treated a maximum of three attacks. Analysis of variance or the Student t test and chi-square or Fisher exact tests were used for univariate comparisons. Hochberg corrections were used for multiple-group comparisons. A generalized estimating equation method was used to correct for within-subject correlation. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. RESULTS: Two hundred thirty-one patients (84% women) treated 589 evaluable migraine attacks (sumatriptan, n = 135; naratriptan, n = 90; zolmitriptan, n = 149; rizatriptan, n = 149). Triptan tablet consumption per attack (mean +/- SD) for rizatriptan (1.24 +/- 0.56) was significantly lower than that of sumatriptan (1.75 +/- 1.2; P< .05), zolmitriptan (1.61 +/- 0.86; P < .05), or naratriptan (1.46 +/- 0.62; P= .05). The average number of triptan tablets taken and additional medication use increased according to baseline pain severity. More attacks were treated with one tablet of rizatriptan (81.2%) than with one tablet of sumatriptan (51.9%), zolmitriptan (55.7%), or naratriptan (60%). The probability of using more than one triptan tablet per attack (24 hours) was more than three times greater for sumatriptan (adjusted OR = 3.71; CI, 2.05 to 6.7; P = .001) and zolmitriptan (adjusted OR = 3.32; CI, 1.82 to 6.17; P = .001), and more than two times greater for naratriptan (adjusted OR = 2.66; CI, 1.36 to 5.21; P =.004) than for rizatriptan. CONCLUSIONS: Rizatriptan was associated with significantly lower triptan tablet use and additional medication use per attack than the other triptans. Additional randomized studies are needed to confirm the conclusions of this study.

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Characteristic	Lamisil® (terbinafine)	Sporanox® (itraconazole)	Griseofulvin
Pharmacology	Inhibits squalene oxidase (which will block biosynthesis of ergosterol). Ergosterol is an essential component of fungal cell membranes.	Inhibits the cytochrome P450-dependent synthesis of ergosterol. Ergosterol is an essential component of fungal cell membranes.	An antibiotic derived from a species of *Penicillium*, griseofulvin is fungistatic. It is deposited in keratin precursor cells; it has a greater affinity for diseased tissue. Griseofulvin binds to the new keratin, making it resistant to fungal invasion.
Manufacturer	Novartis	Jansen-Ortho	
Date of FDA approval	May 10, 1996	September 11, 1992	
Generic available?	No	No	Previously there have been generics available. Currently there are availability issues with the generics.
Dosage forms / route of admin	Capsule - 250 mg	• 100 mg capsule for oral administration • 10 mg/ml oral solution • 10 mg/ml injection for IV infusion (Ortho Biotech)	Microsize • tablets – 250 mg, 500 mg • oral suspension – 125 mg/5 ml Ultramicrosize • tablets - 125 mg, 165 mg, 250 mg 330 mg
General Dosing guidelines	• Onychomycosis of fingernails – 250 mg qd x 6 weeks • Onychomycosis of toenails – 250 mg qd x 12 weeks	• Onychomycosis of fingernails – 2 pulses of 250 mg bid for 1 week, with 3 weeks between pulses • Onychomycosis of toenails ± fingernails – 250 mg qd x 12 weeks	Onychomycosis of fingernails • Microsize – 1 gm QD x 4 months • Ultramicrosize – 660 mg or 750 mg QD x 4 months Onychomycosis of toenails • Microsize – 1 gm QD x 6 months • Ultramicrosize – 660 mg or 750 mg QD x 6 months
Pediatric Labeling	Safety and efficacy have not been established in pediatric patients.	Limited information available for use of - • Solution in children 6 months and up • Capsules in children 3 years and up	Age 2 and older for other indications

Characteristic	Lamisil® (terbinafine)	Sporanox® (itraconazole)	Griseofulvin
FDA Labeled Indications	Treatment of onychomycosis of the toenail or fingernail caused by dermatophytes.	In non-immunocompromised patients • Onychomycosis • In immunocompromised and non-immunocompromised patients • Blastomycosis, pulmonary and extra-pulmonary • Histoplasmosis • Aspergillosis, pulmonary and extra-pulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy	• Tinea capitis • Tinea corporis • Tinea pedis • Tinea unguium (onychomycosis) • Tinea cruris • Tinea barbae
Contraindications	Hypersensitivity to terbinafine or any of its components.	• Itraconazole should not be used to treat onychomycosis in patients with CHF or a history of CHF. • Coadministration with quinidine, triazolam, midazolam, pimozide, dofetilide, cisapride. • Hypersensitivity to itraconazole or any of its components. • HMG-CoA reductase inhibitors metabolized by CYP3A4 (eg. Lovastatin, simvastatin). • Treatment of onychomycosis in pregnancy or in women contemplating pregnancy.	• Hypersensitivity to griseofulvin • Porphyria • Hepatocellular failure • Pregnancy or intent to become pregnant within one month from stopping therapy
Drug interactions	Cimetidine, rifampin, caffeine, cyclosporine, dextromethorphan. Terbinafine inhibits CYP2D6-mediated metabolism.	See contraindications (above). cyclosporine, digoxin, oral hypoglycemics, protease inhibitors, warfarin, tacrolimus, zolpidem, calcium channel blockers (also some reports of increased edema), buspirone, carbamazepine, phenytoin and vinca alkaloids.	Oral contraceptives, warfarin, phenobarbital, cyclosporine, salicylates

Characteristic	Lamisil® (terbinafine)	Sporanox® (itraconazole)	Griseofulvin
Major AEs/Warnings	• Most common – headache, rash, diarrhea, dyspepsia, nausea, liver enzyme abnormalities. • Rare cases of liver failure – some resulting in death or liver transplant. • Changes to the ocular lens and retina – clinical significance of these changes is not known. • Isolated cases of neutropenia – reversible when terbinafine discontinued. • Rare reports of serious skin reactions (including Stevens-Johnson syndrome). If a skin rash occurs and is progressive, then discontinue treatment. • Use of terbinafine is not recommended in patients with a creatinine clearance = 50 ml/min. • Use not recommended in chronic or acute hepatic impairment. • Pregnancy: Category B • The use of terbinafine in nursing mothers is not recommended.	• Most common – nausea, vomiting, diarrhea, rash, headache, edema, hypertension, fatigue • Most common reported on onychomycosis clinical trials – elevated liver enzymes, gastrointestinal disorders, rash, hypertension, hypertriglyceridemia • Rare cases of liver failure – some resulting in death or liver transplant. • Neuropathy – if neuropathy occurs, discontinue itraconazole therapy • Use of itraconazole is not recommended in patients with a creatinine clearance = 30 ml/min. • Pregnancy: Category C • The use of itraconazole in nursing mothers is not recommended. • With continuous use > 1 month – monitoring of LFTs is recommended. • For patients at risk for hypokalemia and on high dose itraconazole, periodic serum potassium levels are recommended.	• Most common – diarrhea, nausea, vomiting, headache, rash, urticaria, photosensitivity • Males should wait at least 6 months after completing therapy to father a child • Lupus-like syndromes or exacerbation of lupus erythematosus • Pregnancy: Category C • Use not recommended in nursing women.

Characteristic	Lamisil® (terbinafine)	Sporanox® (itraconazole)	Griseofulvin
Pharmacokinetics issues	• Well absorbed, first pass metabolism significantly decreases bioavailability (to about 40%). • Administration with food slightly increases bioavailability (AUC increased by < 20%).	• Cannot use the solution and the capsules interchangeably (increased bioavailability with the solution). • The capsules should be taken after a full meal. • The solution should be taken on an empty stomach. • Grapefruit juice may reduce bioavailability of itraconazole. • Decreased absorption with decreased gastric acidity (PPIs, H2 antagonists and antacids).	• Absorption can very from person to person (there are "poor absorbers" that consistently have lower blood levels). • A high fat meal increases the rate, but not the extent, of absorption. • The absorption of the ultramicrosize is 1.5 times more efficient than the microsize (so 2/3 of the dose of the ultramicrosize is needed). There is no evidence this causes any significant clinical differences in safety or efficacy.
Dosage adjustment in key populations	Patients with cirrhosis or renal impairment (creatinine clearance = 50 ml/min) have shown a 50% decrease in terbinafine clearance. Use in these patients is not recommended.	• Elderly – use is recommended in the elderly only if the potential benefits outweigh the potential risks. • Pediatric use – limited information with pediatric use – safety and efficacy have not been established.	Pediatrics – ultramicronized dose – 3.3 mg/lb per day
Place in therapy	Short-term oral itraconazole and oral terbinafine therapy were found to be similar in efficacy and adverse effects in a randomized, double-blind comparative study for the treatment of toenail onychomycosis. There were less treatment-related serious adverse events in the itraconazole patients compared with the terbinafine patients, and more terbinafine-treated patients discontinued therapy permanently due to adverse events. Another trial (LION study), a long-term outcomes assessment, showed superior efficacy for terbinafine, though both groups had high relapse rates (21% for terbinafine and 48% for itraconazole).		Treatment of choice for tinea capitis infections in children. In treatment of onychomycosis, the duration of treatment is less for terbinafine. In a clinical comparison, terbinafine had better efficacy and a lower incidence of adverse effects compared to griseofulvin

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GUIDELINES **Guidelines for treatment of onychomycosis** D.T. Roberts, W.D. Taylor* and J. Boyle.

Summary: These guidelines for management of onychomycosis have been prepared for dermatologists on behalf of the British Association of Dermatologists. They present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.

THE FOLLOWING IS EXCERPTED FROM Pp 405-407.

Griseofulvin. Griseofulvin (Fulcin®; Grisovin®; GlaxoSmithKline, Uxbridge, U.K.) is weakly fungistatic, and acts by inhibiting nucleic acid synthesis, arresting cell division and inhibiting fungal cell wall synthesis. It is available in tablet form and is the only antifungal agent licensed for use in children with onychomycosis, with a recommended dose for age groups of 1 month and above of 10 mg kg^{1} daily. It requires to be taken with fatty food to increase absorption and aid bioavailability. In adults the recommended dose is 500 mg daily given for 6-9 months in fingernail infection and 12-18 months in toenail infection. Mycological cure rates in fingernail infection are reasonably satisfactory at around 70% but griseofulvin is a disappointing drug in toenail disease where cure rates of only 30-40% can be expected.[16]

It is generally recognized that 500 mg daily is too small a dose for nail infection and 1 g daily is most often prescribed, but there is no certain evidence that this improves cure rates in toenail infection. Although the cost of griseofulvin is very low, its poor cure rate, often necessitating further treatment, suggests that its cost/efficacy ratio is relatively high. Both direct and historical comparison with studies of the newer antifungal agents terbinafine and itraconazole suggest that griseofulvin is no longer the treatment of choice for dermatophyte onychomycosis.

Side-effects include nausea and rashes in 8-15% of patients. In adults, it is contraindicated in pregnancy and the manufacturers caution against men fathering a child for 6 months after therapy.

Terbinafine. Terbinafine (Lamisil®; Novartis, Camberley, U.K.), an allylamine, inhibits the enzyme squalene epoxidase thus blocking the conversion of squalene to squalene epoxide in the biosynthetic pathway of ergosterol, an integral component of the fungal cell wall. Its action results in both a depletion of ergosterol, which has a fungistatic effect, together with an accumulation of squalene, which appears to be directly fungicidal. The minimum inhibitory concentration (MIC) of terbinafine is very low, approximately 0·004 μg mL^{1}. This is equivalent to the minimal fungicidal concentration (MFC), demonstrating that this drug is truly fungicidal *in vitro*. It is the most active currently available antidermatophyte agent *in vitro* and clinical studies strongly suggest that this is also the case *in vivo*.

Itraconazole. Itraconazole (Sporonox®; Janssen-Cilag, High Wycombe, U.K.) is active against a range of fungi including yeasts, dermatophytes and some nondermatophyte moulds. It is not as active *in vitro* against dermatophytes as terbinafine, its MIC being 10 times greater. Although it is generally felt to be a fungistatic agent it can achieve fungicidal concentrations, although its MFC is about 10 times higher than its MIC.

Both terbinafine and itraconazole persist in the nail for a considerable period after elimination from the plasma. This property has given rise to a novel intermittent ('pulsed') treatment regimen using itraconazole in nail infection.

Terbinafine vs. itraconazole in dermatophyte onychomycosis. Both of these drugs have been shown to be more effective than griseofulvin in dermatophyte onychomycosis and therefore the optimum choice of treatment lies between terbinafine and itraconazole.

Terbinafine is licensed at a dose of 250 mg daily for 6 weeks and 12 weeks in fingernail and toenail infection, respectively. Itraconazole is licensed at a dose of 200 mg daily for 12 weeks continuously, or alternatively at a dose of 400 mg daily for 1 week per month. It is recommended that two of these weekly courses, 21 days apart, are given for fingernail infections and three courses for toenail disease.

There have been numerous open and placebo-controlled studies of both drugs in dermatophyte nail infection. However, historical comparisons of such studies do not provide evidence of equivalent quality as that achieved by directly comparative double-blind trials, as even in properly conducted studies the results can be influenced by

variation in the criteria for mycological
or clinical cure, or by the period of follow-up. It is generally accepted that patients entered into such studies should be both microscopy- and culture-positive for fungus and that mycological cure should be defined as microscopy and culture negativity at completion. Clinical criteria for cure are difficult to interpret as the appearance of the nail prior to infection is generally unknown and, especially in the case of toenails, because trauma can affect their appearance. Short follow-up periods after cessation of therapy are unlikely to allow interpretation of which is the superior drug; a follow-up period of at least 48 weeks (preferably 72 weeks) from the start of treatment should be allowed both in order to allow the most effective preparation to become apparent and to identify relapse as far as possible.

There are various published studies comparing terbinafine with continuous itraconazole therapy, most of which demonstrate terbinafine to be the more effective agent. Thus far there are only two studies comparing terbinafine with intermittent itraconazole therapy. The first compared terbinafine 250 mg daily for 16 weeks with four 'pulses' of itraconazole 400 mg daily for 1 week in every 4 weeks for 16 weeks and also with terbinafine 500 mg daily for 1 week in every 4 weeks for 16 weeks. As only approximately 20 patients were recruited in each study group, this was a very small study; the regimens used were not those of the U.K. product licences, and the results comparing the groups were not significantly different. A more recent and much larger study has been completed comparing terbinafine 250 mg daily for both 3 and 4 months with itraconazole 400 mg daily for 1 week 3 and 1 week **Error! Bookmark not defined.**4. One hundred and twenty patients were recruited to each group and the follow-up period was 72 weeks. The study was carried out in double-blind, double-placebo fashion and demonstrated terbinafine 250 mg daily for both 3 and 4 months to be very significantly superior to both three and four 'pulses' of itraconazole (*Strength of recommendation A, Quality of evidence I*;

The 151 patients in the Icelandic arm of this study were further studied for long-term effectiveness of treatment during a 5-year blinded prospective follow-up study. At the end of the study mycological cure without a second therapeutic intervention was found in 46% of the 74 terbinafine-treated subjects but in only 13% of the 77 itraconazole-treated subjects. Mycological and clinical relapse was significantly higher in the itraconazole group (53% and 48%) than the terbinafine group (23% and 21%) (*Strength of recommendation A, Quality of evidence I*).

The superiority of terbinafine has recently been supported by a systematic review of oral treatments for toenail onychomycosis; this reference documents many additional studies and also the varied and often incompletely presented criteria that have been used to describe a 'clinical cure'.

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Terbinafine: a review of its use in onychomycosis in adults.

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Terbinafine, an orally and topically active antimycotic agent, inhibits the biosynthesis of the principal sterol in fungi, ergosterol, at the level of squalene epoxidase. Squalene epoxidase inhibition results in ergosterol-depleted fungal cell membranes (fungistatic effect) and the toxic accumulation of intracellular squalene (fungicidal effect). Terbinafine has demonstrated excellent fungicidal activity against the dermatophytes and variable activity against yeasts and non-dermatophyte molds in vitro. Following oral administration, terbinafine is rapidly absorbed and widely distributed to body tissues including the poorly perfused nail matrix. Nail terbinafine concentrations are detected within 1 week after starting therapy and persist for at least 30 weeks after the completion of treatment. Randomized, double-blind trials showed oral terbinafine 250 mg/day for 12 or 16 weeks was more efficacious than itraconazole, fluconazole and griseofulvin in dermatophyte onychomycosis of the toenails. In particular, at 72 weeks' follow-up, the multicenter, multinational, L.I.ON. (Lamisil vs Itraconazole in ONychomycosis) study found that mycologic cure rates (76 vs 38% of patients after 12 weeks' treatment; 81 vs 49% of recipients after 16 weeks' therapy) and complete cure rates were approximately twice as high after terbinafine treatment than after itraconazole (3 or 4 cycles of 400 mg/day for 1 week repeated every 4 weeks) in patients with toenail mycosis. Furthermore, the L.I.ON. Icelandic Extension study demonstrated that terbinafine was more clinically effective than intermittent itraconazole to a statistically significant extent at 5-year follow-up. Terbinafine produced a superior complete cure rate (35 vs 14%), mycologic cure rate (46 vs 13%) and clinical cure rate (42 vs 18%) to that of itraconazole. The mycologic and clinical relapse rates were 23% and 21% in the terbinafine group, respectively, compared with 53% and 48% in the itraconazole group. In comparative clinical trials, oral terbinafine had a better tolerability profile than griseofulvin and a comparable profile to that of itraconazole or fluconazole. Post marketing surveillance confirmed terbinafine's good tolerability profile. Adverse events were experienced by 10.5% of terbinafine recipients, with gastrointestinal complaints being the most common. Unlike the azoles, terbinafine has a low potential for drug-drug interactions. Most pharmacoeconomic evaluations have shown that the greater clinical effectiveness of oral terbinafine in dermatophyte onychomycosis translates into a cost-effectiveness ratio superior to that of itraconazole, fluconazole and griseofulvin. CONCLUSION: Oral terbinafine has demonstrated greater effectiveness than itraconazole, fluconazole and griseofulvin in randomized trials involving patients with onychomycosis caused by dermatophytes. The drug is generally well tolerated and has a low potential for drug interactions. Therefore, terbinafine is the treatment of choice for dermatophyte onychomycosis.

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Terbinafine in fungal infections of the nails: a meta-analysis of randomized clinical trials.

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BACKGROUND: Historically, there has been a general resistance to treating onychomycosis on the basis that such treatments were protracted and of uncertain outcome. However, modern treatments act more promptly and reliably. OBJECTIVES: To carry out a meta-analysis to evaluate the efficacy and safety of terbinafine in comparison with placebo, itraconazole and griseofulvin. METHODS: The analysis used data from published trials, supplemented where necessary by reference to the original trial reports. RESULTS: Three trials were included in which terbinafine was compared with placebo. From four trials comparing terbinafine with itraconazole, a statistically significant advantage in favour of terbinafine was observed for negative culture and microscopy at the end of the trials. Furthermore, both patients and physicians reported terbinafine to be better tolerated than itraconazole. From two trials comparing terbinafine with griseofulvin, a significantly higher rate of negative microscopy and culture was observed with terbinafine. CONCLUSIONS: A significant advantage in favour of treatment with terbinafine was observed.

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Long-term efficacy of antifungals in toenail onychomycosis: a critical review.

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BACKGROUND: Modern antifungal drugs achieve high mycological and clinical cure rates in onychomycosis of the toes, but little is known about the long-term evolution of the treated patients. OBJECTIVES: The aim of this review was to analyse the therapeutic results recorded more than 1 year after initiation of therapy. METHODS: We used two endpoints for the analysis: EP1 (the number of patients with negative mycology after follow-up, divided by the number of patients included at day 0, including all patients lost to follow-up), and EP2 (the number of patients with negative mycology after follow-up divided by the number of patients with negative mycology at week 48). Clinical cure rate (EPclin) was the number of patients clinically cured or with minimal residual lesions divided by the number of patients included at day 0. RESULTS: From a Medline search we identified 17 studies providing results beyond 48 weeks. Ketoconazole 200 mg d(-1) up to 1 year resulted in EP1 of 11% at 18 months, and EP2 of 43%. Griseofulvin 1 g d(-1) for 1 year allowed an EP1 of 43% at 18 months, and EP2 of 71%. The mean EP1 after fluconazole once weekly up to 1 year was 49% at 18 months, and EP2 was 91%. With itraconazole 200 mg d(-1) or 400 mg d(-1) for 1 week each month for 3-4 months, EP1 was 37% at 18 months, and 53% at 2 years; EP2 was 76% at 4 years. Terbinafine 250 mg d(-1) for 12-16 weeks achieved an EP1 of 62% at 18 months, 72% at 2 years, and 60% at 4 years; EP2 was 80% at 18 months, 81% at 2 years, and 71% at 4 years. In the only study planned to compare the long-term efficacy of terbinafine and itraconazole, EP1 at 18 months was significantly higher with continuous terbinafine than with intermittent itraconazole (66% vs. 37%, $P < 0.001$). The clinical cure rates were 21% at 60 weeks and 37% at 72 weeks with fluconazole. EPclin was 27% at 18 months and 35% at 2 years with itraconazole. EPclin was 48% at 18 months, 69% at 2 years and 50% at 4 years with terbinafine. CONCLUSIONS: Considering the stringency of the criteria we used, this critical review suggests that the long-term efficacy achieved with terbinafine is superior to that obtained with griseofulvin, ketoconazole, fluconazole or itraconazole.

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Oral treatments for toenail onychomycosis: a systematic review.

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OBJECTIVE: To identify and synthesize the evidence for the efficacy of oral treatments for fungal infections of the toenails. DESIGN: Systematic review of randomized controlled trials. INTERVENTIONS: Oral treatments for dermatophyte infections of the toenails. MAIN OUTCOME MEASURES: Cure confirmed by microscopy and culture results in patients with clinically diagnosed fungal infections. Data relating to the clinical cure rates were also extracted from the trials. RESULTS: A pooled analysis of 2 trials comparing mycological cure rates from continuous treatment with terbinafine (250 mg/d for 12 weeks) and continuous treatment with itraconazole (200 mg/d for 12 weeks) found a statistically significant difference in 11- and 12-month outcomes in favor of terbinafine (risk difference, -0.23 [95% confidence interval, -0.32 to -0.15]; number needed to treat, 5 [95% confidence interval, 4 to 8]). An analysis of clinical cure rates was not possible because of the diversity of definitions used in researching the effectiveness of oral antifungal drugs for onychomycosis. Only 3 trials gave a clear definition of clinical cure and presented data for these outcomes. CONCLUSIONS: There is good evidence that a continuous regimen of terbinafine (250 mg/d) for 3 months is the most effective oral treatment for fungally infected toenails. Consensus among researchers evaluating oral antifungal drugs for onychomycosis is needed to establish meaningful definitions of clinical cure. Most trials were funded by the pharmaceutical industry; we found little independent research, and this may have introduced bias to the review.

TABLES FROM THIS ARTICLE:

Table 1. Oral Antimycotic Treatments vs Placebo

Study, y	Treatment (Dose, mg/d)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/ NNT (95% CI)*
Elewski et al,[13] 1997	Itraconazole (200)	110	12	12	69 (54)	0.6 (0.4 to 0.7)/2 (2 to 3)
	Placebo	104	12	12	6 (6)	
Jones and Zaias,[12] 1996	Itraconazole (200)	36	12	12	24 (69)	0.6 (0.4 to 0.8)/2 (2 to 3)
	Placebo	37	12	12	2 (6)	
Gupta et al,[11] 2000	Intermittent itraconazole (400)	78	12 (1:4)†	48	51 (65)	0.6 (0.5 to 0.7)/2 (2 to 3)
	Placebo	74	12 (1:4)†	48	1 (1)	
Goodfield et al,[14] 1992	Terbinafine (250)	70	12	48	38 (73)	0.5 (0.4 to 0.6)/2 (2 to 3)
	Placebo	29	12	48	1 (6)	
Watson et al,[15] 1995	Terbinafine (250)	56	12	24	33 (59)	0.5 (0.3 to 0.6)/2 (2 to 3)
	Placebo	55	12	24	5 (9)	
Svejgaard et al,[16] 1997	Terbinafine (250)	63	12	12	49 (66)	0.4 (0.2 to 0.5)/3 (2 to 3)
	Placebo	64	12	12	24 (33)	

*CI indicates confidence interval; NNT, number needed to treat.
†For the intermittent schedule, 1:4 indicates 1 week of treatment in every 4 weeks.

Table 2. Oral Antimycotic 4-Arm Trials

Study, y	Treatment (Dose, mg/d)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/ NNT (95% CI)*
Evans and Sigurgeirsson,[17] 1999	Terbinafine (250)	124	12	72	81 (76)	−0.6 (−0.4 to −0.8)/4 (3 to 5)
	Intermittent itraconazole (400)	126	12 (1:4)†	72	41 (38)	
	Terbinafine (250)	120	16	72	80 (81)	0.2 (0.2 to 0.4)/5 (3 to 9)
	Intermittent itraconazole (400)	126	16 (1:4)†	72	53 (49)	
Shemer et al,[10] 1999	Itraconazole (200)	16	12	48	11 (68)	0.18 (−0.4 to 0.5)/NR
	Intermittent itraconazole (200)	16	12 (1:4)†	48	8 (50)	
	Itraconazole (200)	16	16	48	10 (64)	0.8 (0.5 to 1.33)/NR
	Intermittent itraconazole (200)	16	16 (1:4)†	48	10 (64)	
Billstein et al,[39] 1999	Terbinafine (250)	29	12	72	11 (37)	0.4 (0.2 to −0.5)/3 (2 to 5)
	Terbinafine (250)	27	16	72	10 (71)	0.6 (0.5 to 0.8)/3 (2 to 5)
	Terbinafine (250)	26	24	72	17 (94)	0.3 (0.2 to 0.5)/2 (2 to 3)
	Placebo	27	24	72	0	Reference

*CI indicates confidence interval; NNT, number needed to treat; and NR, not reported.
†For the intermittent schedule, 1:4 indicates 1 week of treatment in every 4 weeks.

Table 3. Dose-Finding Studies

Study, y	Treatment (Dosage)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/ NNT (95% CI)*
Alpsoy et al,[18] 1996	Terbinafine (250 mg/d)	24	12	48	19 (79)	0.5 (–0.2 to 0.2)/NR
	Intermittent terbinafine (250 mg/d)	23	12 (1:3)†	48	17 (74)	
Tausch et al,[19] 1997	Terbinafine (250 mg/d)	72	6	48	43 (59)	0.1 (–0.02 to 0.2)/NR
	Terbinafine (250 mg/d)	76	12	48	55 (72)	
De Doncker et al,[20] 1996	Intermittent itraconazole (200 mg/d)	25	12 (1:4)†	24	16 (64)	0.08 (–0.2 to 0.3)/NR
	Intermittent itraconazole (200 mg/d)	25	16 (1:4)†	24	18 (72)	
Havu et al,[21] 1997	Itraconazole (200 mg/d)	62	12	52	41 (66)	0.03 (–0.13 to 0.2)/NR
	Intermittent itraconazole (200 mg/d)	59	12 (1:4)†	52	41 (69)	
Drake et al,[22] 1997	Terbinafine (250 mg/d)	140	12	48	98 (70)	0.2 (0.1 to 0.3)/NR
	Terbinafine (250 mg/d)	142	24	48	124 (87)	0.6 (0.5 to 0.7)/NR
	Placebo	71	24	48	6 (9)	Reference
Van der Schroeff et al,[23] 1992	Terbinafine (250 mg/d)	30	6	48	12 (41)	0.1 (–0.1 to 0.3)/NR
	Terbinafine (250 mg/d)	34	12	48	24 (71)	0.4 (0.2 to 0.6)/NR
	Terbinafine (250 mg/d)	34	24	48	28 (82)	Reference
Ling et al,[24] 1998	Fluconazole (150 mg/wk)	78	16	15	24 (34)	0.2 (0.1 to 0.4)/4 (3 to 7)
	Fluconazole (150 mg/wk)	84	26	15	40 (49)	0.3 (0.1 to 0.4)/4 (3 to 6)
	Fluconazole (150 mg/wk)	86	39	15	46 (61)	0.5 (0.3 to 0.6)/2 (2 to 3)
	Placebo	83	39	15	6 (8)	Reference
Scher et al,[25] 1998	Fluconazole (150 mg/wk)	89	12 (Maximum)	18	38 (53)	0.2 (0.1 to 0.4)/3 (2 to 5)
	Fluconazole (300 mg/wk)	88	12 (Maximum)	18	42 (59)	0.3 (0.2 to 0.5)/3 (3 to 5)
	Fluconazole (450 mg/wk)	92	12 (Maximum)	18	47 (61)	0.3 (0.2 to 0.5)/3 (3 to 4)
	Placebo	92	12 (Maximum)	18	12 (16)	Reference

*CI indicates confidence interval; NNT, number needed to treat; and NR, not reported.
†For the intermittent schedule, 1:3 and 1:4 indicate 1 week of treatment in every 3 and 4 weeks, respectively.

Table 4. Oral Antimycotic 2-Arm Trials

Study, y	Treatment (Dose, mg/d)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/ NNT (95% CI)*
Svejgaard,[26] 1985	Ketoconazole (200)	9	45.9 (Average)	Not clear	1 (11)	0.1 (0.09 to 0.3)/9 (3 to ∞)†
	Griseofulvin (500)	7	38.1 (Average)	Not clear	0	
Cullen and Cullen,[27] 1987	Ketoconazole (200)	14	24	24	5 (35)	−0.05 (−0.4 to 0.3)/NR
	Griseofulvin (1000)	12	24	24	5 (42)	
Piepponen et al,[28] 1992	Itraconazole (100)	31	24-36	40	10 (37)	0.08 (−0.13 to 0.31)/NR
	Griseofulvin (500)	30	24-36	40	7 (30)	
Walsoe et al,[29] 1990	Itraconazole (100)	9	24	24	0	−0.004 (−0.17 to 0.18)/NR
	Griseofulvin (500)	10	24	24	0	
Brautigam et al,[30] 1995	Terbinafine (250)	86	12	52	70 (81)	0.18 (0.05 to 0.31)/6 (4 to 21)
	Itraconazole (200)	84	12	52	53 (63)	
Arenas et al,[31] 1995	Terbinafine (250)	27	12	36	23 (100)	0.19 (−0.02 to 0.4)/NR
	Itraconazole (200)	26	12	36	17 (100)	
De Backer et al,[40] 1996	Terbinafine (250)	186	12	48	119 (73)	0.2 (0.1 to 0.3)/5 (4 to 8)
	Itraconazole (200)	186	12	48	77 (46)	
Baran et al,[32] 1997	Terbinafine (250)	62	52	52	47 (90)	−0.1 (−0.2 to 0.04)/5 (2 to 4)
	Griseofulvin (1000)	58	52	52	37 (69)	
Faergenann et al,[33] 1995	Terbinafine (250)	43	16	52	36 (84)	0.3 (0.1 to 0.5)/3 (2 to 6)
	Griseofulvin (500)	41	52	52	19 (45)	
Hofmann et al,[34] 1995	Terbinafine (250)	83	24	72	52 (81)	0.1 (0.001 to 0.2)/NR
	Griseofulvin (1000)	88	24	72	42 (62)	
Honeyman et at,[9] 1997	Terbinafine (250)	64	16	52	61 (95)	0.1 (0.01 to 0.2)/10 (5 to 143)
	Itraconazole (200)	70	16	52	59 (83)	
Kavli et al,[35] 1984	Ketoconazole (200)	14	16	24	4 (28)	0.2 (−0.09 to 0.5)/NR
	Ketoconazole (200) + urea cream	15	16	24	8 (53)	

*CI indicates confidence interval; NNT, number needed to treat; and NR, not reported.
†NNT with an infinite CI is a point estimate; it includes the possibility of no benefit or harm.

Table 5. Oral Antimycotic 3-Arm Trials

Study, y	Treatment (Dose, mg/d)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/ NNT (95% CI)*
Korting et al,[36] 1993	Griseofulvin (660)	36	78	77	2 (6)	0.02 (−0.08 to 0.1)/NR
	Griseofulvin (990)	36	78	77	2 (6)	0.02 (0.8 to 0.1)/NR
	Itraconazole (100)	36	78	77	3 (8)	Reference
Haneke et al,[37] 1998	Itraconazole (200)	538	26	26	238 (76)	−0.17 (−0.1 to 0.2)/6 (5 to 9)
	Itraconazole (200)	450	12	12	222 (74)	−0.2 (−0.1 to 0.2)/5 (4 to 7)
	1% Miconazole cream	363	26	26	97 (60)	Reference
Tosti et al,[38] 1996	Intermittent terbinafine (500)	21	16 (1:4)†	43	16 (80)	−0.09 (−0.3 to 0.15)/NR
	Intermittent itraconazole (400)	20	16 (1:4)†	43	15 (75)	−0.01 (−0.27 to 0.25)/NR
	Terbinafine (250)	19	16	43	16 (94)	Reference

*CI indicates confidence interval; NNT, number needed to treat; and NR, not reported.
†For the intermittent schedule, 1:4 indicates 1 week of treatment in every 4 weeks.

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Facts and Comparisons, Copyright 2002.

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First Health Services Corporation

Glaucoma Agents: Carbonic Anhydrase Inhibitors – Topical Agents		
Brand Name **Generic Name**	**Trusopt®** **(Dorzolamide)**	**Azopt®** **(Brinzolamide)**
Pharmacology	Dorzolamide and brinzolamideare carbonic anhydrase inhibitors for ophthalmic use. Carbonic anhydrase(CA) is an enzyme found in many tissues of the body, including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, CA exists as a number of isoenzymes, the most active being CA-II, found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of CA in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP). Dorzolamide and brinzolamide reduce elevated IOP by inhibiting CA-II. Elevated IOP is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.	
Manufacturer	Merck	Alcon
Date of FDA approval	December 9,1994	April 1, 1998
Patent Expirations[1]	April 28, 2008	October 24, 2012
Generic formulation available?	No	No
Dosage forms / route of admin	2% solution, In 5 and 10 mL *Ocumeters* Preservative: 0.0075% benzalkonium chloride, hydroxyethylcellulose, sodium hydroxide, and mannitol	Suspension: 1% In 2.5, 5, 10, and 15 mL *Drop-Tainers*. Preservative: 0.01% benzalkonium chloride, mannitol, carbomer 974P, tyloxapol, sodium chloride, hydrochloric acid and/or sodium hydroxide, and EDTA.
Dosing frequency	TID	BID - TID
Generalized Dosing Guidelines	Dosage: One drop in the affected eye(s) 3 times daily.	Dosage: One drop in the affected eye(s) 3 times daily.
Storage	Store at 15° to 30°C (59° to 86°F). Protect from light.	Store at 4° to 30°C (39° to 86°F). Shake well.

First Health Services Corporation

Glaucoma Agents: Carbonic Anhydrase Inhibitors – Topical Agents		
Brand Name Generic Name	**Trusopt® (Dorzolamide)**	**Azopt® (Brinzolamide)**
FDA Labeled Indications	Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma	Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Pediatric Labeling	▪ Safety and efficacy in children have not been established. ▪ Topical CAI, Trusopt® and Azopt® have been used in pediatric glaucoma and have a safe systemic safety profile, but appear to be less effective in decreasing IOP than oral acetazolamide (whose administration is limited due to side-effects in pediatric patients). ▪ Topical CAIs appear to be safe, but less effective than topical beta-blockers in the treatment of pediatric glaucoma	
Other studied uses	None	None
Contraindications	Documented hypersensitivity (including sulfonamide sensitivity)	Documented hypersensitivity (including sulfonamide sensitivity)
Drug interactions	▪ Carbonic anhydrase inhibitors, oral ▪ Amphetamines or Mecamylamine or Quinidine ▪ Silver preparations, ophthalmic, such as silver nitrate	▪ Carbonic anhydrase inhibitors, oral
Major AEs / Warnings	Ocular burning, stinging or discomfort; Bitter taste; Superficial punctate keratitis; Signs and symptoms of ocular allergic reaction; Blurred vision; Tearing dryness; Photophobia	▪ Blurred vision; Bitter, sour or unusual taste; Blepharitis; Dermatitis; Dry eye; Foreign body sensation; Headache; Hyperemia; Ocular discharge, discomfort, keratitis, pain, and pruritus; Rhinitis ▪ Less burning, stinging or discomfort compared with Trusopt.
Pharmacokinetics issues	Peak- 2 hours	N/a
Dosage adjustment in key populations	CrCl< 30 mL/min not recommended	

First Health Services Corporation

Glaucoma Agents: Carbonic Anhydrase Inhibitors – Topical Agents		
Brand Name **Generic Name**	**Trusopt®** **(Dorzolamide)**	**Azopt®** **(Brinzolamide)**
Pipeline	▪ Xalacom® (Xalatan/Timolol combination) made by Pharmacia is not yet approved in the U.S. but is expected to compete against against Cosopt® (Dorzolamide and Timolol) combination. ▪ ISTALOL(TM) (made by ISTA in a joint agreement between ISTA and Senju Pharmaceuticals) is a unique, once-a-day, proprietary liquid formulation of the FDA-approved beta-blocker, timolol, to treat glaucoma. On July 28,2003, the FDA issued an approvable letter for Istalol™. According to Ista the product will be launched in early 2004. ▪ Neuroprotective strategies aimed to inhibit activated pathways that invoke retinal ganglion cell death in glaucoma (optic nerve damage and blindness) appear to be the strategies for glaucoma therapy in the future. In particular, inhibition of NMDA and calcium channels are targets of clinical investigation. 1. NMDA-receptor antagonists : Memantine has been studied as a neuroprotective agent in glaucoma. (Namenda ®(memantine) was recently approved for use in Alzheimer's Disease) 2. Nitrous oxide synthase inhibitors 3. Neurotrophic factors 4. Substances which bind free radicals 5. Glutamate-releasing inhibitors 6. Caspase inhibitors 7. Calcium Channel Blockers: short acting orals have been studied ▪ Antifibrotic agents such as 5-FU and Mitomycin C used in conjunction with surgery to prevent fibrotic changes that may occur with wound healing. ▪ Nipradilol (beta-blocker with alpha blocking activity) ▪ CAT-152; Lerdelimumab (MFT=CAT, UK based company) a fully human monoclonal antibody against TGF(B)2, designed to prevent post-operative scarring in patients undergoing surgery for glaucoma. ▪ Bunazosin HCL (property of Eisai) the first selective 8_2 blocker that stabilizes intraocular pressure ▪ DE-085: originally licensed to Asahi Glass, a prostaglandin based treatment for glaucoma. ▪ Lomerizine HCL (DE-090): originally licensed to Nippon Organon, an oral calcium antagonist with the ability to improve intraocular circulation ▪ Olmesartan (Benicar®): the only ARBII in development as a glaucoma treatment.	

First Health Services Corporation

Glaucoma Agents: Carbonic Anhydrase Inhibitors – Topical Agents		
Brand Name **Generic Name**	**Trusopt®** **(Dorzolamide)**	**Azopt®** **(Brinzolamide)**
Comparisons	▪ Azopt® and Trusopt® appear to be comparable for the treatment of elevated intraocular pressure. Azopt® is claimed to cause less burning and stinging upon instillation than Trusopt® due to pH differences (7.5 and 5.6 respectively) in the formulations; however, it is felt that more data are needed before conclusions/claims can be made regarding this claim. ▪ Trusopt® (Dorzolamide) and Azopt® (brinzolamide), which are relatively specific inhibitors of carbonic anhydrase enzyme II, reduce IOP by 15 to 26%. Additional reductions in IOP are seen with the topical CAIs when combined with other classes of antiglaucoma agents.	

[1] Patent Expiration is dependent upon existing and changing patent law and subsequent litigation in pursuant to such.

First Health Services Corporation

Glaucoma Agents: Combination Products (CAI and BB)

Brand Name **Generic Name**	**Cosopt® solution** **(dorzolamide 2%/timolol 0.5%)**
Pharmacology	See individual agents
Manufacturer	Merck
Date of FDA approval	April 7, 1998
Patent Expiration[1]	April 17, 2011
Generic formulation available?	No
Dosage forms / route of admin	Dorzolamide 2% and timolol 0.5% per mL, in 5 and 10 mL *Ocumeters* **Preservative: 0.0075% benzalkonium chloride and mannitol.**
Storage	Store between 15° and 25°C (59° to 77°F). Protect from light
Dosing frequency	BID
General Dosing Guidelines	Instill one drop into the affected eye(s) two times daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart.
FDA Labeled Indications	Treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-adrenergic blocking agents
Pediatric Labeling	See individual agents
Other studied uses	Dorzolamide (Macular edema and glaucoma and ocular hypertension associated with pseudoexfolliation)
Contraindications	Documented hypersensitivity; Asthma, bronchial, or history of or Chronic obstructive pulmonary disease, severe; Cardiac failure, overt or Cardiogenic shock or Heart block, 2nd or 3rd degree atrioventricular (AV) or Sinus bradycardia
Drug interactions	Beta-adrenergic blocking agents, systemic; Calcium channel blocking agents, oral or intravenous; Carbonic anhydrase inhibitors, systemic; Catecholamine-depleting medications, such as reserpine; Digitalis; Quinidine; Salicylates, high doses
Major AEs / Warnings	History of atopy; Bronchospastic disease, or history of (other than bronchial asthma, or history of); Chronic obstructive pulmonary disease, mild or moderate; Bronchitis, chronic; Emphysema; Diabetes mellitus, especially labile diabetes; Hypoglycemia; Hepatic function impairment; Hyperthyroidism; Myasthenia gravis; Renal function impairment, severe (CRCL < 30 mL/min)
Pharmacokinetics issues	None
Dosage adjustment in key populations	CrCl< 30 mL/min not recommended

First Health Services Corporation

Glaucoma Agents: Combination Products (CAI and BB)

Brand Name **Generic Name**	**Cosopt® solution** **(dorzolamide 2%/timolol 0.5%)**
Pipeline Agents	See above
Comparisons	Only combination CAI and BB available; will be competing in the future with Xalacon® (PA/BB combination) for efficacy and utilization. Combination of CAI and BB appears to be synergistic in lowering IOP

[1] Patent Expiration is dependent upon existing and changing patent law and subsequent litigation in pursuant to such.

First Health Services Corporation

Cost-minimisation study of dorzolamide versus brinzolamide in the treatment of ocular hypertension and primary open-angle glaucoma: in four European countries.

Rouland JF, Le Pen C, Gouveia Pinto C, Berto P, Berdeaux G.
Pharmacoeconomics. 2003;21(3):201-13.

Hopital Huriez, Service d'Ophtalmologie, Lille Cedex, France.

OBJECTIVE: Cost is an issue when prescribing two drugs with equivalent efficacy. We compared the direct medical costs of topical brinzolamide 1% (twice a day or three times daily) with topical dorzolamide 2% (twice a day or three times daily) in France, Italy, Portugal and Spain in patients with ocular hypertension or primary open-angle glaucoma.

DESIGN AND SETTING: Three double-blind, controlled, randomised trials (with a study duration of 3 months) compared the response rate of brinzolamide twice a day or three times daily versus dorzolamide three times daily, and the response rate of brinzolamide-timolol twice a day versus a dorzolamide-timolol combination twice a day. A fourth double-blind randomised trial (with a duration of 12 months) compared brinzolamide twice a day and three times daily with timolol monotherapy. Local tolerance was compared in two dedicated studies. Rates of switching to a new medication regimen were evaluated through a US health maintenance organisation database. In case of treatment failure, the patients were treated with latanoprost. A model was developed to value direct medical costs over 3 months. The economic perspective was that of the third-party payer and the patient, and included direct medical costs (reimbursed part plus co-payment). PATIENTS: Patients with ocular hypertension and/or primary open-angle glaucoma who had not responded to or could not tolerate beta-blocker therapy.

OUTCOME MEASURE: The daily direct medical costs of therapy with the two drugs.

RESULTS: As monotherapy, brinzolamide twice daily and three times daily was found to be as efficacious as dorzolamide three times a day. Brinzolamide twice daily plus timolol was also as efficacious as a combination of dorzolamide and timolol twice a day. Stinging of the eye upon instillation with brinzolamide was experienced by fewer patients than with dorzolamide ($p < 0.0001$). The likelihood of patients treated with dorzolamide changing therapy was 1.28 times greater than that for those treated with brinzolamide. The size of the brinzolamide drop is 18.7% smaller than that of dorzolamide allowing seven more therapy days per bottle with brinzolamide twice daily than with dorzolamide monotherapy, and five more days when brinzolamide is used three times a day. The direct medical costs for patients treated with brinzolamide were lower in all four European countries when drop size was taken into account than for those treated with dorzolamide. Sensitivity analyses confirmed the robustness of our findings.

CONCLUSION: Because brinzolamide can be prescribed twice daily in monotherapy and because fewer patients treated with brinzolamide switch therapy due to local intolerance, our model suggests that brinzolamide is a cost-saving alternative to dorzolamide.

Patients' acceptance of a switch from dorzolamide to brinzolamide for the treatment of glaucoma in a clinical practice setting.

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Clin Ther. 2000 Oct;22(10):1204-12.

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BACKGROUND: The first topically active carbonic anhydrase inhibitor, dorzolamide, was developed to circumvent the adverse systemic effects of oral carbonic anhydrase inhibitors. However, its use has been associated with ocular discomfort.

OBJECTIVE: The present study examined the acceptability of brinzolamide, as measured by patients' ratings and stated preferences, in patients with glaucoma previously treated with dorzolamide in the clinical practice setting.

METHODS: This was a prospective, open-label, noncomparative study conducted shortly after the approval of brinzolamide. Ophthalmologists in private practice in the continental United States were asked to select patients currently using dorzolamide as their sole or combination therapy for glaucoma. Patients underwent a screening assessment in which they were asked to rate their ocular comfort with dorzolamide on a scale from 1 to 6. Brinzolamide was then substituted for dorzolamide, and patients returned for a follow-up visit approximately 1 to 3 months later. At this visit, patients were asked about ocular comfort, their preferred medication, and whether they thought ocular comfort influenced their adherence to treatment. Intraocular pressure (IOP) was measured at both visits.

RESULTS: Valid visit dates (ie, both baseline and follow-up dates) were available for 447 of 501 patients from 68 of 73 sites (range, 1-40 patients per site). Because not all measurements were available for all patients at each visit, the sample size varied for each measurement. Demographic data were not available. The switch to brinzolamide resulted in a mean decrease in IOP of approximately 0.8 mm Hg ($P < 0.001$, paired t test). Sixty-nine percent of patients (274/397) reported an improvement of > or =1 grade in their comfort rating with brinzolamide versus dorzolamide. The mean (+/- SD) improvement in comfort rating was 1.43 +/- 1.48 grades ($P < 0.001$, Wilcoxon rank sum test). When patients were asked whether their adherence to treatment was affected by the occurrence of burning and stinging, 43% (173/399) answered affirmatively. Fifty-nine percent (251/424) preferred brinzolamide to dorzolamide. At the end of the study, based on patient preference, physician judgment, and other factors, 73% of responding patients (301/410) continued with brinzolamide therapy.

CONCLUSIONS: In this study, the switch from dorzolamide to brinzolamide resulted in overall improvements in comfort and ocular hypotensive efficacy. However, studies using a more rigorous randomized, controlled, crossover design are needed to support these observations.

Publication Types: Clinical Trial , Multicenter Study

First Health Services Corporation

Comparison of topical brinzolamide 1% and dorzolamide 2% eye drops given twice daily in addition to timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension.

Michaud JE, Friren B; International Brinzolamide Adjunctive Study Group.
Am J Ophthalmol. 2001 Aug;132(2):235-43.

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PURPOSE: The aim was to compare topical brinzolamide 1% twice daily with dorzolamide 2% twice daily, each given with timolol 0.5% twice daily, for safety and effects on intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension. METHODS: This double-blind, randomized, active controlled, parallel group study was conducted multinationally at 31 sites, in 241 patients as above, with assessments at baseline and monthly during 3 months of treatment. The primary end point was a diurnal reduction of trough/peak intraocular pressure from a timolol 0.5% twice daily baseline. RESULTS: Both treatment regimens reduced intraocular pressure significantly at all time points (P <.001): brinzolamide plus timolol by -3.6 to -5.3 mm Hg (-14.2 to -21.9%), dorzolamide plus timolol by -3.6 mm Hg to -5.1 mm Hg (-14.1 to -21.2%). Clinically relevant intraocular pressure reductions (decreases 5 mm Hg or greater or absolute intraocular pressure values 21 mm Hg or less) were manifested by 50.0% to 89.3% of patients under brinzolamide plus timolol and by 43.9% to 85.4% under dorzolamide plus timolol. The treatments were equivalent in mean intraocular pressure-lowering. In general, both regimens were well tolerated. However, more patients (P =.001) experienced at least one adverse event with dorzolamide plus timolol (32.8%) as compared with brinzolamide plus timolol (14.7%); also, more patients (P =.001) experienced ocular discomfort (stinging and burning) after dorzolamide plus timolol (13.1%) than after brinzolamide plus timolol (1.7%). CONCLUSIONS: In terms of intraocular pressure reduction, brinzolamide 1% twice daily was equivalent to dorzolamide 2% twice daily, each added to timolol 0.5% twice daily, but brinzolamide produced significantly less ocular burning and stinging.

Publication Types:

- Clinical Trial
- Multicenter Study

First Health Services Corporation

- Randomized Controlled Trial